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Editorial

Medical-Student Research — The Medical Students Who Aren't There

SHORTLY after Roentgen discovered the X-ray, the N-ray was described. During the next several years a sizable literature developed from many different laboratories, comparing X-rays and N-rays. Methods were devised for distinguishing the two emanations, and a number of important differences in physical properties and biological effects were described. It was not until nearly 10 years and many papers later that it was conclusively shown that X-rays and N-rays were the same. The N-ray vanished.

Today there are two types of medical students: those preparing themselves for the practice of medicine and following the conventional medical school curriculum, and those who, in addition to regular course work, are taking part in research training, positioning themselves, they hope, for careers in investigative medicine. The difference between the two is exceedingly sharp. Stipends are available from the Public Health Service, the voluntary health agencies, and many other sources for the latter, none for the former. The two types have been counted, and 40 per cent of 1959 medical school graduates fell into the research-trainee group.[1] They have been compared with respect to economic background, paternal profession, marital status, and many other properties;[2] and deans proudly announce increasing percentages of research trainees in their student bodies. The distinction appears to be sharpest of all for the medical students themselves. They see two different ways of life before them between which they must make a seemingly irrevocable choice; some 25 per cent announce they are preparing themselves for the road to academic medicine in one form or another.[2]

Everyone seems confident there is a difference; everyone, that is, except the educators themselves. For no matter how you define research trainng (and definitions are numerous: the teaching of experimental design, offering laboratory experiences in problem solving, teaching the technologies of investigation, stimulating the qualities of curiosity and inquiry in the medical student, teaching the intellectual content of medicine as contrasted with its practical content, etc.), the educators insist that all these are components of good teaching in any course of the regular curriculum.[3-6] To the educator, there is no difference between research training, properly conceived, and the remainder of the curriculum, properly conducted. In their view, the experiences of the research trainee are not qualitatively different (or, at least, should not be different) from those of his non-researching classmate. And the medical student researcher —like the N-ray—does not exist.

The reason why deans, medical students, and educators see this differently is that each is looking at a different facet. To certain student research trainees—and not to their

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dishonor—it simply means more income (about 10 per cent of their year's expenses[1]). Presumably it is preferred to more gainful occupations such as laundry delivery or television repairing because, they trust, it is more relevant for their subsequent professional careers. And even if it be an ordeal, it has its propitiatory and "salting" aspect, since the faculty will always view the research trainee approvingly. For other students, it stands for a career or, more particularly, for a type of person. Not knowing what "research" is, (the pragmatism of the student is similar to that of the promotions committee—research is that activity which leads to publication) and not realizing that the career of an investigator often is no less a career-in-evolution than his own, the student pictures an ascetic, modestly salaried, brilliant man in a laboratory—easily differentiated from the man in private practice.

On the other hand, the dean sees research as a space-occupying, appurtenanced devotional that enhances the reputation and income of the school but plays no major role in its accreditation. The period of time the medical student elects to spend in research is agreeably viewed by him as those months when the medical student is not a medical student. The investigator to whom the medical student is apprenticed sees it in still another light. He welcomes it as an opportunity to transmit private skills and enthusiasms; and there is the possibility, if all goes well, of finishing the current project earlier by virtue of the eager extra hands.

In this caricaturized picture of research training for the medical student, the only one who looks at its content for the student is the educator. He sees research as the inquiring, creative aspect of medicine, and the months the medical student spends in a research laboratory are simply a focused, particularized sampling of what should pervade the entire curriculum. Research, for him, is an activity that takes place at the interface between science and the "art," the intuitive, the unknown in Medicine. For him, the physician using intelligence and imagination to solve a patient's problem at the bedside may be as much a researcher as the man in the laboratory.

Which view is correct? With increasing numbers of students wishing to participate and with ever increasing funds for stipends (in 1959 more than $2.2 million were available from all sources[1]), isn't it time we decided what this experience is for? If the educator is correct, how should the laboratory experience be designed? Should the emphasis be on technologic training? Should provisions be made for training in background sciences such as mathematics and instrumentation? If so, by whom? Beyond the technical skills, what attitudes should it engender, and what is the best way to do this?

In several schools thought has already been given to these and other questions, and many different approaches are being developed that tend to affirm the educator's point of view. In Seattle, the summer courses in mathematics, statistics, and electronics, which were at first designed for the research trainees, now attract many faculty members and are also offered to pre-freshman medical students for the summer months before they start medical school. At a school in Michigan, faculty members from five different clinical and preclinical departments who are engaged in research in vascular and blood pressure problems have pooled their student-training resources; they select two freshman medical students each year to join the group on a year-round, stipended, research-participation basis; the students are graduated each year to the research activities of the faculty member in a department related to the curriculum for that year; they have their own seminars attended by the students from all 4 years and the participating faculty members. In several schools there are schemes for year-round research participation with the trainees paid a stipend on an hourly basis for holidays, week ends, etc., the belief here being that the usual 3 summer-months' experience is neither very enduring nor very profitable. In Oregon, a 4-year, year-round program of research participation in the cardiovascular field constructed along

tutorial lines is offered selected freshman students. Many schools have encouraged activities that bring together the students apprenticed to different laboratories for journal clubs, science clubs, mathematics courses, etc.

If research participation is accepted as a valuable part of undergraduate education—which seems to be the trend—the investigator in the research laboratory is undertaking an obligation when he accepts a student into his laboratory, not simply offering an opportunity. But only when we have decided what the research experience is supposed to do to the student—rather than what the student is supposed to do to the research project—can we determine where it belongs in the curriculum and whether these students who irregularly people our laboratories are outrageously underpaid technicians, or are an elite vaguely headed for positions of academic leadership, or are simply a student body being optimally prepared for the scientific medicine of tomorrow.

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The Early History of Instrumental Precision in Medicine

We have all come to admit gratefully the value of specialisation in medicine; but he who is watchful over the general interests of his profession must have seen that this subdivision of labour involves for us perils, which are seen on the one side by the general practitioner, and on the other by those who, in a large-minded way, pursue limited lines of work. Medicine does not grow in an even fashion. When watching a saline solution under the lens, you observe some brilliant crystal shoot out in advance and hold its place until the rest, more slowly but surely, join or pass it, you see an image of that which continually illustrates medical progress. Today it is surgery which wins; a few years ago it was ophthalmology, which in newly acquired precision and in predictive accuracy and therapeutic gains, set up for us novel standards of exactness and, enriching our symptomatology, cast light in many directions. The mere physician seemed to be hopelessly left behind, but now again it is pure medicine which has gone to the front.—S. WEIR MITCHELL, M.D., *Transactions of the Congress of American Physicians and Surgeons,* Second Triennial Session held at Washington, D.C., 1891. New Haven, The Congress, 1892, p. 160.

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The Clinical, Hemodynamic, and Pathologic Diagnosis of Muscular Subvalvular Aortic Stenosis

By HERMANN MENGES, JR., M.D., ROBERT O. BRANDENBURG, M.D., AND ARNOLD L. BROWN, JR., M.D.

STENOSIS of the outflow tract of the left ventricle is a disease of serious and often of fatal consequence. The form of obstruction varies, but most commonly it is a discrete ridge of fibrous tissue that projects into the left ventricle completely encircling the outflow tract.[1] In some instances this fibrous ridge may be accompanied by bulging and hypertrophy of the underlying interventricular septum.[2-4] Recently, several authors have reported muscular hypertrophy of the septum and left ventricle alone as a cause of subvalvular aortic stenosis.[2, 5-10] They suggest that during systolic contraction this thickened muscle comes together, narrowing the outflow area and impeding ventricular ejection.

In 1958 Teare[11] reported postmortem findings in eight relatively young people who had had what he termed "asymmetrical cardiac hypertrophy." In each instance there was diffuse hypertrophy of the interventricular septum and anterior left ventricle. Shortly thereafter, Brock[5] described six cases of hypertrophy of the left ventricle and upper muscular septum with resultant functional obstruction to left ventricular outflow. Bercu and associates[6] added a similar case in which a systolic gradient existed between the left ventricle and aorta and at necropsy only hypertrophy of the musculature of the outflow tract was evident.

In early 1960 Brent and associates[7] described a number of patients with this same entity. They emphasized the familial incidence of the disease, since all of their six patients having proved muscular subaortic stenosis were members of only two families. Brachfeld and Gorlin[2] reviewed the subject of subaortic stenosis and reported two cases with predominantly muscular obstruction. Goodwin and associates[8] suggested the name "obstructive myocardiopathy," stating that this massive muscular hypertrophy could obstruct the inflow and outflow of blood in both the right and left ventricles. Most recently, Braunwald and co-workers[12] presented a study of 14 patients who had a condition that the authors called "idiopathic hypertrophic subaortic stenosis." Their recognition of the similarities in many previously reported cases, coupled with their own experience, enabled them to elucidate this entity.

Recently, we have reviewed all the cases at the Mayo Clinic in which a diagnosis of subaortic stenosis was made either at operation or at necropsy. This is a report of those cases in which diffuse muscular thickening of the interventricular septum and wall of the left ventricle resulted in obstruction of left ventricular outflow.

Materials and Methods

Eight cases of proved muscular subvalvular aortic stenosis have been reviewed. In three cases necropsy was performed, while in five cases the diagnosis was established at operation. The clinical evaluation includes data on the patient's history, physical examination, electrocardiogram, roentgenograms, and cardiac catheterization. In view of the difficulty of recognizing obstruction of left ventricular outflow of this "functional" muscular variety, both the thickness of the left ventricle and the width of the interventricular septum were measured in the necropsy specimens. The entire muscular septum was cut in a vertical section beginning at the commissure of the right and posterior coronary cusps. A point 1.5 cm. down from the junction of the muscular and membranous septum was arbitrarily selected, and here the width of the septum was measured. The left ventricular meas-

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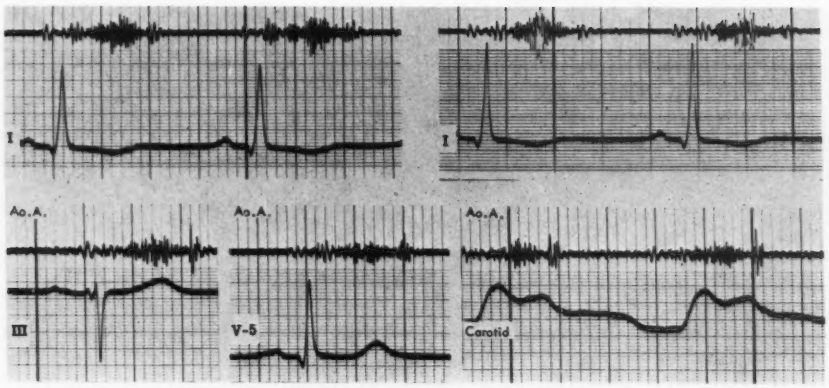

Figure 1

Phonocardiogram (case 6). Note character of the murmur, the third and fourth heart sounds, and the bisferious character of the carotid pulse tracing.

urement was taken at a point of average thickness as suggested by Saphir.[13] The septal width was then divided by the thickness of the left ventricle in an attempt to establish a ratio between the two.

A control series of 50 hypertrophied hearts and 20 apparently normal hearts were evaluated similarly. These hearts were selected in consecutive order at necropsy.

Sections for microscopic study were taken from the area of obstruction and from a similar area in the control group. These sections were prepared with hematoxylin and eosin and elastic van Gieson stains.

Results

Clinical

General Data. Six patients were males and two were females. Their ages were as follows: 17, 20, 23, 35, 36, 37, 47, and 59 years.

History. None had a history of rheumatic fever. A murmur was first noted at ages 6, 12, 14, 20, 29, 36, 39, and 47 years, respectively. Similarly, symptoms began at ages 12, 19, 21, 30, 34, 36, 44, and 46 years. Six patients had a history suggestive of angina. All eight patients had dyspnea on exertion, and two had a history compatible with frank congestive heart failure. One died suddenly at home (59 years of age), while two men, 35 and 36 years of age, died after operation. A review of the family histories revealed heart disease in two instances: The mother of the 17-year-old boy had died suddenly at 51 years of age of a heart condition of undetermined nature. Similarly, the mother of the 20-year-old girl had died unexpectedly at 39 years of age of heart disease and diabetes.

Physical Findings. All eight patients had a systolic murmur described as grade 3 or 4 (basis of 1 to 4) and harsh, although in three instances a higher pitched component to the murmur was audible. In seven, the murmur was heard best at the fourth to fifth left intercostal spaces and in one it was heard equally well at the right second interspace and along the left sternal border. The murmur in seven patients was heard well in the aortic area, but in only five was it heard over the vessels of the neck. No patient had a diastolic murmur. The aortic second sound was decreased in one and was normal in seven. Seven patients had a palpable thrill—in six it was in the fourth left interspace and in one, at the suprasternal notch. Blood pressure was normal in all eight. A narrow splitting of the second sound, heard in three instances, was loudest in the right second interspace. Change in the width of the splitting was not detectable during phases of respiration, nor did a phonocardiogram taken in one case disclose any alteration in the width with breathing. An apical third heart sound was audible in three cases. In one patient the phonocardiogram confirmed the presence of this sound and in addition disclosed a fourth heart sound (fig. 1). Atrial fibrillation oc-

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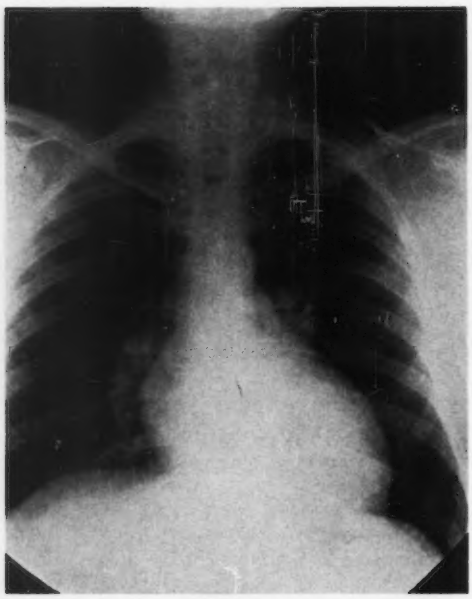

Figure 2

X-ray evidence of left atrial enlargement (case 4).

curred periodically in the 59-year-old man, but no others demonstrated any irregularities in rhythm.

Electrocardiogram. In seven of the eight patients the electrocardiograms were interpreted as left ventricular hypertrophy of the pressure overload type. One disclosed a left bundle-branch block. Left atrial enlargement was noted in two.

Roentgenogram. Posteroanterior and oblique views of the thorax disclosed evidence of left ventricular enlargement in all cases. Left atrial enlargement was present in three cases (fig. 2). In no patient was there x-ray evidence of a calcified aortic valve or dilatation of the ascending aorta (fig. 3).

Cardiac Catheterization. This procedure was carried out in seven instances. In only three cases, however, were left ventricular withdrawal tracings obtained. Each withdrawal tracing demonstrated a zone of reduced systolic pressure in the outflow area of the left ventricle (fig. 4). Systolic gradients across the region of the aortic valve in the seven cases varied from 64 to 135 mm. In every instance an anacrotic notch was evident on the ascending limb of the left ventricular pressure curve. In six of the seven cases the aortic curve showed a rapid upsweep of the percussion wave (less than 0.13 second) with a delayed or bisferious form and a good dicrotic notch (fig. 5). In the seventh instance central arterial pulse tracings were not recorded. Ventricular end diastolic pressures were elevated in five of the seven cases. The highest was 29 mm. and the lowest, 18 mm. Equivocally elevated pulmonary artery pressures were noted in the two instances in which they were recorded. Left atrial contraction waves also were noted in these two cases. In five cases a single extrasystole and compensatory pause could be demonstrated. The systemic arterial tracings in each of these revealed that the beat that followed the compensatory pause had a smaller pulse pressure than the control values for that patient (fig. 6).

In one patient an angiocardiogram displayed an area of narrowing in the outflow tract of the left ventricle. This narrowing appeared to increase during ventricular systole (fig. 7).

Pathologic Findings

Five patients were treated surgically and specific measurements of the septum and left ventricle were not obtained. All five had gross muscular hypertrophy of the upper muscular septum with obstruction to the left ventricular outflow tract. In addition, the left ventricle in each patient was greatly thickened.

At necropsy the hearts of three men who died at ages 59, 35, and 36 years weighed 720, 780, and 930 Gm., respectively; the normal weight in each case would have been 262, 214, and 382 Gm.* The left ventricles measured 1.8, 1.7, and 2.0 cm. while the right ventricles measured 0.5, 0.5, and 0.6 cm. Septal hypertrophy subjectively was graded as 4 (basis of 1 to 4) in all cases. In one case (59-year-old man) the upper septum bulged signifi-

*Normal weights were determined with reference to age and weight of patient.[24]

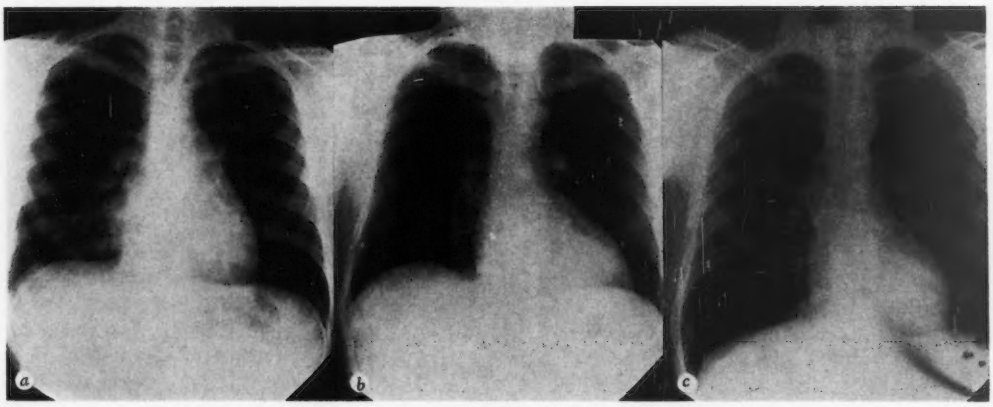

Figure 3

Subvalvular aortic stenosis. a. *Case 1.* b. *Case 7.* c. *Man 24 years of age with congenital aortic valve stenosis. Note aortic dilatation in* c *and absence of this in* a *and* b.

cantly so that it formed a ledge at the junction of the muscular and membranous septa (fig. 8). In the other two cases the upper septum showed diffuse thickening but with less bulging of the superior edge. In the three cases the thickness 1.5 cm. from the junction of the muscular and membranous septa was 2.8, 3.0, and 3.1 cm. The ratio of the septal width to the left ventricular thickness in these three cases was 1.55, 1.76, and 1.55 (figs. 9 and 10). The heart of the older man (case 8) disclosed evidence of healed endocarditis of the mitral valve.

Subvalvular sclerosis, grade 3, was noted in each of the three patients; however, no fibrous ridge was evident. Coronary artery sclerosis was grade 1 in two cases and grade 2 in the third case. There were no associated anomalies. In one case there was microscopic evidence of a minimal increase in connective tissue within the muscular septum. Each showed a thickened hyalinized endocardial surface and the cardiac muscle appeared normal (fig. 11).

Control Group

All 20 normal hearts weighed between 240 and 460 Gm. Each was within normal limits with respect to the weight and age of the patient. The thickness of the left ventricle varied between 1.0 and 1.5 cm., the average being 1.3 cm. The septal width 1.5 cm. down from the junction of the muscular and membranous septa measured from 1.0 to 1.4 cm. with an average of 1.2 cm. The ratio of the septal width to the left ventricular thickness was calculated in each case with the average ratio being 0.95 (fig. 9).

The weights of the 50 hypertrophied hearts ranged from 500 to 1,122 Gm. The thickness of the left ventricle varied between 1.1 and 2.0 cm., the average being 1.7 cm. The mean width of the upper muscular septum was 1.65 cm., with a range of 1.0 to 3.0 cm. The average ratio of the septal width to the thickness of the left ventricle was 0.98. This ratio exceeded 1.25 in a single instance, that of a 38-year-old man with a calcified stenotic aortic valve that was thought to be bicuspid. The septum was grossly thickened with a small left ventricular cavity. The septum measured 3.0 cm. and the left ventricle 2.0 cm. with a ratio of 1.5. Microscopic sections of the upper interventricular septum were interpreted as normal in both the control and the hypertrophied group.

Discussion

Symptoms and Signs

Muscular obstruction of the left ventricle has become increasingly important as a potentially operable form of heart disease. Most

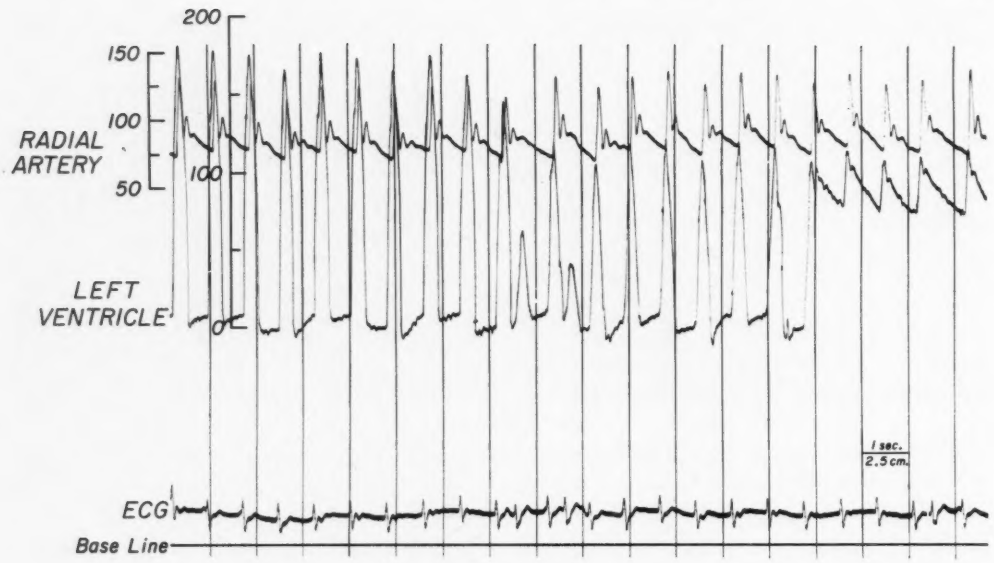

Figure 4

Cardiac catheterization tracing in 49-year-old white man diagnosed clinically as having muscular subvalvular aortic stenosis. Note infundibular pressure zone, left ventricular anacrotism and pulsus alternans. (The patient was not one of the series of eight described in this paper.)

commonly, the symptoms are dyspnea and angina, although lightheadedness and palpitations have been reported with some frequency. Congestive heart failure may occur and sudden death is not uncommon. Often one may elicit a family history of heart disease. In this series symptoms became evident between the second and fifth decades, although younger patients with this disease have been reported.[10, 12] A harsh, "diamond-shaped" murmur, much like that heard in aortic valve stenosis, is invariably present along the lower left sternal border. The murmur may have a higher pitched component, and clinically, mitral insufficiency is frequently suspected. Transmission of the murmur to the vessels of the neck occurred in more than half of the cases in this study, although other authors have suggested that this is uncommon.[12] A systolic thrill is felt oftenest along the left sternal border, but it may be detected in the suprasternal notch.

The second sound in the aortic area is usually of normal intensity. The absence of an ejection click in all of these cases supports the recent observations of Hancock[15] that this phenomenon does not occur in muscular obstruction. Paradoxical splitting of the second sound would be expected and was present with some frequency in one series.[12] Although a split second sound was noted in several of these cases, there was no detectable change in the width of the splitting during phases of respiration. It should be re-emphasized that paradoxical splitting may be obscured if the sound of pulmonic valve closure is masked by the prolonged systolic murmur.[12] Our experience as well as that of Braunwald and coworkers[12] suggested that a diastolic murmur would make the diagnosis of muscular outflow obstruction unlikely. Apical third and fourth heart sounds may be heard, but phonocardiography should be employed to detect sounds that are clinically inaudible. Atrial fibrillation, although rare, does occur. There were no patients in our series with elevated blood

pressure or other diseases that might have predisposed to cardiac hypertrophy.

Roentgenograms and Electrocardiograms

The absence of aortic valvular calcification and poststenotic dilatation of the ascending aorta have been used previously as diagnostic aids to distinguish valvular from subvalvular aortic stenosis.[2, 16, 17] The younger age of some patients with diffuse muscular obstruction makes the absence of calcium in the aortic valve a less significant guide. A normal appearing ascending aorta, however, is of great diagnostic help. Advanced left ventricular hypertrophy is a constant x-ray finding, and frequently left atrial enlargement is suspected. Similarly, the electrocardiogram discloses an enlarged left ventricle and not uncommonly it suggests left atrial hypertrophy.

Anomalous atrioventricular excitation, although reported in one series,[12] was not found in any of our preceding cases. The experience of other authors, in addition to our experience in one case mentioned herein, indicates that angiocardiography is a reliable method of demonstrating the region of obstruction.[12]

Hemodynamics

The diagnosis of muscular subvalvular obstruction can be confirmed accurately by cardiac catheterization. The most reliable criterion is the presence of a zone of reduced systolic pressure in the infundibulum of the left ventricle (table 1). As the catheter is withdrawn across the narrowed outflow area the systolic pressure drops, but the diastolic pressure remains unchanged. When the aortic valve is traversed, the diastolic pressure rises but systolic levels remain unaltered. This phenomenon also has been described in patients with proved fibrous subaortic stenosis. Not uncommonly, a small gradient also may occur between the right ventricle and the pulmonary artery.

Consistently, in this series, a notch appeared on the ascending limb of the left ventricular pressure tracing. The exact mechanism for this phenomenon is not clear. It may be that blood is ejected at the inception of systolic contraction, as it is in the normal heart. However, with the approximation of the hypertrophied septum and left ventricle, an obstruction develops. This causes a momentary delay in ejection until greater systolic force can overcome the obstruction. This brief pause creates the left ventricular anacrotic notch. Braunwald and associates[12] expressed the opinion that this anacrotic notch may signify a delayed onset of contraction of the sphincteric outflow tract.

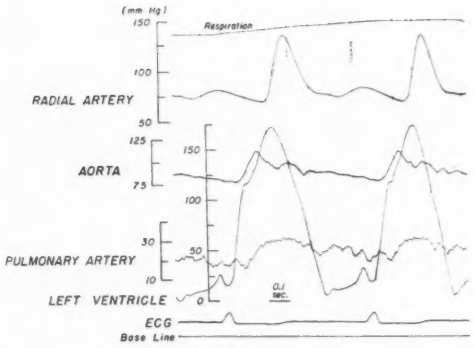

Figure 5

Cardiac catheterization tracings showing anacrotic notch on left ventricular pressure tracing and bisferious aortic pulse (case 1).

Unlike the prolonged ascent of the central arterial pulse in aortic stenosis, patients with muscular obstruction demonstrate a rapid systolic upstroke. Commonly, the aortic curve has a secondary peak or what Brachfeld and Gorlin[2] called a "tidal wave" form. The sharp systolic upsweep and the initial peak occur with early systolic contraction. Obstruction (with the resulting trough) follows and then the delayed ejection of blood occurs causing the secondary or tidal form.

After an extrasystole and a compensatory pause, five patients in this study exhibited a compensatory beat which in each case had a smaller pulse pressure than the control values for that patient. This is in contradistinction to the normal heart, in which one would anticipate a larger pulse pressure in the compensatory beat. Brockenbrough and Braunwald[18] considered this phenomenon to be diagnostic of muscular subvalvular aortic obstruction. They postulated that the greater contractile

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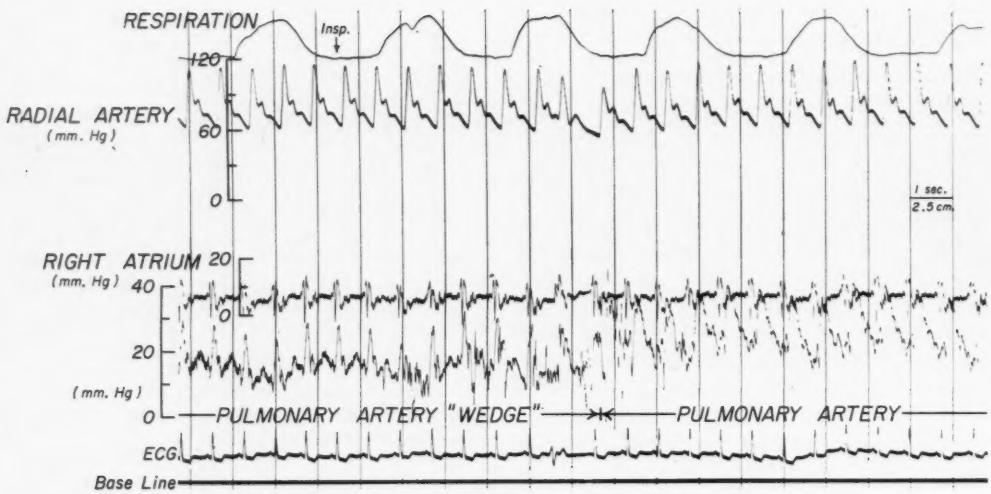

Figure 6

Cardiac catheterization tracings showing small compensatory beat after extrasystole (case 6).

Table 1

*Hemodynamic Data**

Case	Age, yr.	Sex	Pressure, mm. of mercury					Small compensatory beat
			Left ventricle	Infundibular zone	Aorta	Right ventricle	Main pulmonary artery	
1	17	M	172/5-24	126/15	102/73	38/4	31/17	+
2	20	F	217/8	—	81/51	—	—	—
3	23	F	215/6-10	—	85/58	—	—	—
4	35	M	189/10-27	92/20	104/77	—	—	+
5	36	M	206/13-19	—	96/62 (radial)	—	—	+
6	37	M	209/6-18	—	132/77	45/5	33/17	+
7	47	M	216/8-29	152/17		—	—	+

*One patient, a 59-year-old man, was not catheterized (case 8).

force of the compensatory beat forces the thickened musculature ever closer together. The severity of the outflow obstruction increases and the left ventricular stroke volume is reduced.

Pulsus alternans, an elevated pulmonary artery pressure, and left atrial contraction waves are findings that may occur with varying frequency and degree. Elevated end diastolic pressures in the left ventricle occurred fairly consistently in many of these cases, and may have been, as Braunwald and co-workers[12] suggested, the result of decreased compliance of the left ventricle.

Three patients (only one of whom is included in this study) did not demonstrate a left ventricular-aortic gradient at the time of surgical exploration. Preoperatively each had a significant gradient as well as other characteristic clinical and laboratory evidence of muscular subvalvular obstruction. In one case surgical correction was deferred, but at a later date this patient was examined at the National Heart Institute* where surgical exploration revealed diffuse muscular obstruction. The second patient, who had a clinical diag-

*National Institutes of Health, Bethesda, Maryland.

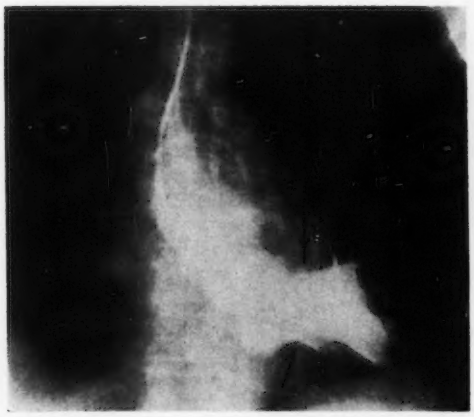

Figure 7

Angiocardiogram (case 7). Area of obstruction indicated by arrows.

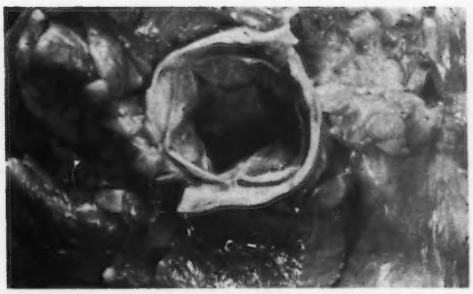

Figure 8

Projection of upper muscular septum into the left ventricular outflow tract as seen from above (case 8).

nosis of mitral insufficiency, was operated on at the clinic. A systolic gradient of 70 mm. had been demonstrated across the region of the aortic valve, but none was evident at the time of operation. The surgical approach through the interatrial septum revealed a normal appearing mitral valve with a mild degree of regurgitation. In retrospect, the classic catheterization findings coupled with persistent symptoms and signs after operation suggest that the primary lesion was actually muscular subaortic obstruction. The third patient was found to have a consistent preoperative gradient of 100 mm. However, this could not be confirmed at operation. Exposure through a left ventricular incision revealed typical muscular subvalvular stenosis.

The reason for the disappearance of the gradient remains elusive. Condon and Lee[19] described a patient with tetralogy of Fallot with infundibular pulmonic stenosis whose obstruction appeared to be relieved by cyclopropane anesthesia. It may be that when the patient is under anesthesia there is a reduction in cardiac output and in the force of systolic contraction. As a result the septum and left ventricle may not become so tightly approximated and the "functional" obstruction may diminish or disappear entirely.

Braunwald and associates[12] noted the association of mitral insufficiency in 11 of the 12 cases of hypertrophic subaortic stenosis. They also found evidence suggesting mitral stenosis in one instance. The mitral valve did not show evidence of disease and this fact was attributed to distortion of the orifice secondary to myocardial hypertrophy. Goodwin and associates[8] also considered inflow obstruction to both ventricles as a manifestation of this disease. Mitral regurgitation was not significant in any of our surgical cases. At necropsy, endocarditis of the mitral valves was detected in one case; in the other two cases the mitral valves appeared normal. An angiocardiogram done in one patient showed a small reflux of contrast media through the mitral orifice into a dilated left atrium. As mentioned previously, one patient was operated on for mitral insufficiency and at a later date was recognized as having muscular subvalvular stenosis. These latter three cases support the premise that mitral valvular dysfunction may coexist with muscular outflow obstruction. However, a consistent, so-called functional regurgitation or stenosis was not apparent.

Pathologic Findings

The large size of the hearts on surgical examination and at necropsy further confirms the seriousness of this disease. The septum in the cases measured was at least one and a half times as thick as the left ventricle, a proportion far beyond that in the normal and hypertrophic hearts of the control group. The

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Figure 9

Muscular subvalvular aortic stenosis (case 4). Note marked increase in width of ventricular septum in contrast to that of normal heart on right. Ruler lies at point of measurement 1.5 cm. from junction of muscular and membranous septa.

Figure 10

Muscular subvalvular aortic stenosis (case 5). Septal width after sectioning measured 3.1 cm.

average ratio of septal width to left ventricular thickness was 1.0, and in only a single instance did it exceed 1.25. This unusual thickness occurred coincidentally in a patient with a stenotic bicuspid aortic valve. In the event that this man had had a successful repair of his aortic valve, a significant residual obstruction probably would have developed.

These measurements indicate that knowledge of the relative width of the muscular septum and left ventricle helps significantly in establishing the diagnosis of muscular subvalvular obstruction. If the septal-ventricular ratio at necropsy exceeds 1.3, the presence of obstruction to left ventricular ejection prior to death should be suspected.

Some anatomic variation was observed in

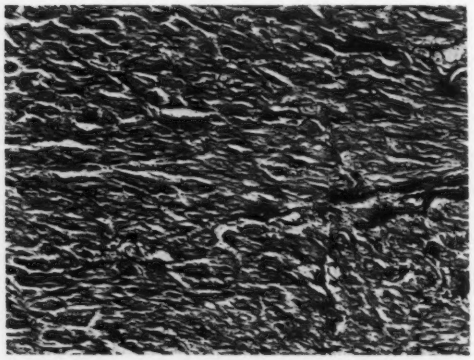

Figure 11

Section of upper muscular septum in case 4 (elastic van Gieson).

the three hearts evaluated at necropsy. In each case the muscular interventricular septum was diffusely thickened and subvalvular endocardial sclerosis was advanced. In one instance, however, the superior aspect of the septum formed a shelf that created the impression of greater apparent bulging of the upper septum into the outflow area. This latter case seems analogous to the concentric hypertrophy of the left ventricular outflow tract described by Brock[5] and appears similar to one of the cases photographed in the series reported by Brent and associates.[7]

Microscopic descriptions of hearts with diffuse muscular obstruction are few. Teare[11] noted alterations in the arrangement of bundles of muscular fibers with variation in size and separation of some by clefts lined with endothelium. Walther and co-workers[10] reported the cases of three young siblings having what appeared to be this same disease. On microscopic examination they noted hypertrophy of individual muscle fibers and areas of focal scarring. Brent and associates[7] found hypertrophy of individual muscle fibers but not the increase in connective tissue described by the others. Only one of the preceding three cases examined microscopically demonstrated any significant abnormality as compared with the control group. In that one case the increase in connective tissue was minimal.

Etiologic Findings

The cause of muscular subvalvular aortic obstruction remains a subject for conjecture. In none of the cases presented herein was there evidence to suggest that prenatal or postnatal factors were contributory. In the absence of any significant microscopic alteration, inflammation also would not seem a probable cause. The early sudden death from heart disease of the mothers of two patients further confirms suggestions previously made in the literature that this may be a familial disease.[7, 9, 10, 12] However, the absence of any familial incidence in the other six cases detracts from this hypothesis.

Braunwald and associates[12] similarly described patients with and without significant family histories. In addition, they reported that murmurs had been heard shortly after birth in three patients; they classified these cases as congenital in origin. Although not included in the preceding series, we also have studied three patients in whom this disease was noted at birth.[20] Clinical studies in two revealed combined subvalvular aortic and infundibular pulmonic stenosis. The third was a stillborn infant. Anatomic evidence of biventricular obstruction of outflow was confirmed in all three—two at necropsy and one at surgical exploration. In each case there was hypertrophy of both ventricles with an enlarged crista supraventricularis and a greatly thickened muscular septum. In the two cases in which specific measurements were obtained the septal-left ventricular ratios were greater than 2. These cases may represent a variant or simply a greater degree of the disease process that produces the muscular obstruction of left ventricle we have described.

It would be an assumption to state that the gross thickening of the septum in these patients represents only cardiac hypertrophy of overwork. The asymmetric distribution of the muscle suggests that the primary abnormality actually may be developmental in origin. Perhaps for reasons unapparent, an abnormal amount of muscle becomes incorporated into the intraventricular ridge as it forms during the second gestational month. As a result, the fully developed septum is unusually wide, and with the obstruction that develops there is secondary myocardial hypertrophy.

Although familial and developmental factors appear to be implicated, present information is not sufficient to draw any positive conclusions as to etiology.

Summary

Muscular obstruction to left ventricular outflow is a rare but serious occurrence. Eight cases in which this disease was anatomically proved are presented. The commonest symptoms are angina, dyspnea, and palpitations. Not uncommonly a family history of heart disease may be elicited. A systolic murmur along the left sternal border is the most characteristic physical finding, but a normal aortic second sound, the presence of third and fourth heart sounds, splitting of the second sound, and the absence of a diastolic murmur are all helpful clinical guides. Withdrawal pressures from the left ventricle reveal a characteristic infundibular pressure zone. Other hemodynamic findings include an anacrotic notch on the left ventricular pressure tracing, a rapidly ascending bisferious aortic pulse and a small compensatory beat after extrasystoles.

Necropsy specimens reveal a grossly thickened interventricular septum as compared with normal and hypertrophied control hearts. Microscopic alterations are minimal. The etiology remains obscure but familial and developmental factors, either or both, appear to be implicated.

Acknowledgment

We wish to thank Dr. Howard B. Burchell and Dr. Jesse E. Edwards for their careful criticism and helpful comments. In addition we are indebted to all of those on the staff of the Section of Pathologic Anatomy who were of assistance.

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It has often been said that, to make discoveries, one must be ignorant. This opinion, mistaken in itself, nevertheless conceals a truth. It means that it is better to know nothing than to keep in mind fixed ideas based on theories whose confirmation we constantly seek, neglecting meanwhile everything that fails to agree with them. Nothing could be worse than this state of mind; it is the very opposite of inventiveness. Indeed a discovery is generally an unforeseen relation not included in theory, for otherwise it would be foreseen.—CLAUDE BERNARD. *An Introduction to the Study of Experimental Medicine.* New York, The MacMillan Company, 1927, p. 37.

The Risk of Interrupting Long-Term Anticoagulant Treatment

A Rebound Hypercoagulable State Following Hemorrhage

By HERBERT S. SISE, M.D., CHRISTOS B. MOSCHOS, M.D., JACQUES GAUTHIER, M.D., AND ROBERT BECKER, B.S.

LONG-TERM anticoagulation is an accepted mode of treatment for prevention of emboli from fibrillating hearts, thrombotic occlusions in arteriosclerotic disorders, and pulmonary emboli in phlebitis. The degree of success in coronary artery disease is somewhat disappointing because it does not completely eradicate death from this cause although the incidence of thrombotic complications is clearly reduced.[1-3] These results, of course, suggest that intravascular coagulation plays a secondary although important role rather than a primary role as postulated by Duguid.[4] The experience acquired during the past 15 years based on laboratory research and clinical observations has led to the establishment of a more or less safe technic of anticoagulant administration. In experienced hands the benefits derived from the use of anticoagulant drugs in carefully selected cases outweighs the risk from bleeding complications due to these drugs. Besides bleeding, as a major complication it has also been noted that discontinuance of treatment for one reason or another carried with it a risk of recurrence of a thrombotic condition. This has been called the rebound phenomenon. In this paper the term "rebound" refers to such post-anticoagulant thrombosis.

Thus, Gosgriff[5] in reporting on anticoagulant treatment in recurrent embolism of cardiac origin observed that of 17 patients who stopped treatment, 12 developed 14 embolic episodes. Eight of them happened within 4 weeks after stopping treatment, the other six between the third and twenty-third month. Further, Keyes, Drake, and Smith[6] noted new infarcts in 14 of 28 patients who stopped anticoagulation during a period of 3 days to 20 months. There were six fatalities. Interruption of treatment in half of the instances was because of hemorrhage. Carter, McDevitt, Gatje, and Wright[7] found a higher tendency to recurrent thromboembolism following discontinuation of anticoagulants within the first 6 weeks, particularly in those with a more pronounced tendency to recurrent thromboembolism or those with congestive heart failure. It is of interest that this incidence of recurrent thromboembolism was higher in the group that stopped anticoagulation than in the group that after a thromboembolic episode remained off anticoagulants. Results of a follow-up study of 293 patients who stopped anticoagulation "for various reasons including hemorrhage" are reported by Nichol et al.[8] A total of 90 patients died of "heart attack"; 20 within the first month and 70 within the subsequent 4 years. In their "discontinued group" of 203 patients, Thomes, Scallen, and Savage[9] noticed a high recurrence rate during the first year after stopping treatment. The longer the treatment the higher was the observed rate of recurrence after stopping. In 13 instances the treatment was discontinued because of bleeding. Of the total, six had a recurrence within the first year after stopping treatment, in four of whom it was fatal. Bjerklund[10] did not notice

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an increase in the mortality rate as compared to the control group when patients stopped treatment after 3 to 5 years. Finally, Dinon and Vander Veer[11] reported on 20 cases with recurrence of acute myocardial infarction within 4 weeks after stopping abruptly or relatively rapidly oral anticoagulation.

These observations suggest that there may be a hypercoagulable state after interrupting long-term anticoagulation. Since it is inevitable that some patients will have to stop treatment for one reason or another, such as bleeding, surgical procedures, other illnesses or some other reason, and thereby expose themselves to a potential risk, this problem was investigated.

Material and Methods

From a consecutive series of 310 patients on long-term anticoagulant treatment with either phenindione or warfarin all patients were collected who had interrupted treatment for any reason and were divided into three groups. Group A consisted of those whose treatment was interrupted because of bleeding. Included were all instances in which the anticoagulant was stopped for 3 days or more, vitamin K_1 in a dose large enough to return the prothrombin time to normal was given, or the patient received a transfusion. Excluded were instances in which the anticoagulant was stopped for 1 or 2 days only. There were 45 instances in 43 patients, two patients having two episodes of bleeding.

Group B consisted of all those who gave up treatment permanently for one reason or another before the end of the period for which they were being treated. The reasons for stopping were either the patient discontinuing of his own choice, treatment discontinued by another medical facility because of a second unrelated disease, an operation in which the conditions did not warrant continuation, patient moved away, was unreliable, or could not get transportation to the laboratory. There were 53 instances in 52 patients, one patient gave up treatment of her own accord twice, but resumed it after the first period of abstinence because of a complication and stopped again.

Group C consisted of all those who stopped treatment temporarily for any reasons other than bleeding. This was predominantly for surgical procedures. There were 38 instances in 28 patients, seven patients more than once because of repeated procedures, usually tooth extractions.

Thromboembolic complications were considered to have happened if the conditions seemed to jus-

Table 1

*Composition of Material**

	Total	Male	Female	Mean age	Diabetes	Hypertension	Coronary heart disease	Cerebral vascular disease	Peripheral embolus	Other
Group A	45 (20)	25 (15)	20 (5)	59 ± 11 (59)	6 (3)	12 (7)	16 (11)	14 (5)	6 (0)	9 (4)
Group B	53 (15)	27 (7)	26 (8)	55 ± 13 (55)	7 (2)	14 (4)	27 (11)	17 (2)	8 (2)	1 (0)
Group C	38 (3)	21 (2)	17 (1)	55 ± 12 (54)	4 (0)	7 (2)	12 (1)	6 (1)	17 (1)	3 (0)
Total	136 (38)	73 (24)	63 (14)		17 (5)	33 (13)	55 (23)	37 (8)	31 (3)	13 (4)

*Figures in parentheses apply to patients who had complications, fatal and nonfatal.

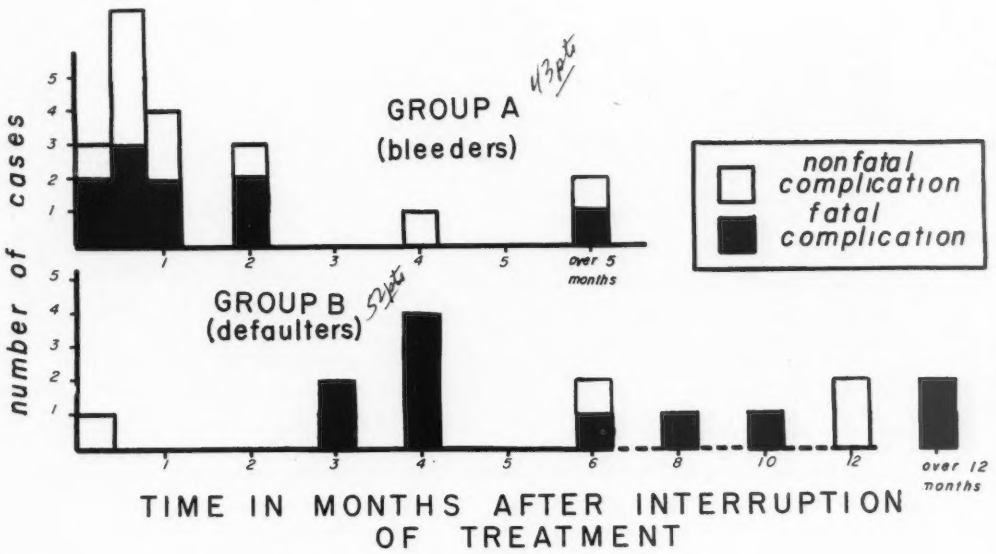

Figure 1

Time intervals between interruption of anticoagulant treatment and appearance of a complication.

tify this conclusion. Death was considered to have been due to a vascular disorder unless the circumstances clearly indicated that it was not. This free interpretation of a complication was necessary because in some instances in which the patient died suddenly at home there was only the history of the event on which to base the diagnosis. Twenty-four of the total of 38 complications were under circumstances in which the diagnosis could be definite (i.e., autopsy, electrocardiogram, paralytic stroke) and in the remaining 14 the diagnosis was empirical.

Details in regard to the composition of the three groups are shown in table 1. They were similar in age distribution, incidence of diabetes, and hypertension. There were a few more women in group B than in the other two groups. More patients were treated for peripheral emboli from the heart in group C and fewer patients were treated for coronary artery disease in group A. Thus, group C is a distinctly different group, but groups A and B are comparable. At least the differences are not sufficient to explain the results noted below.

Results

In group A there were 10 fatal and 10 nonfatal complications. Fourteen of the 20 complications happened within 4 weeks of stopping treatment. This was a distinct difference from groups B and C and suggested a rebound effect.

In group B there were seven fatal and eight nonfatal complications. Only one complication happened in the first 4 weeks, and this was nonfatal.

In group C there were only three complications, all of which were nonfatal. They consisted of an embolus to the leg in one patient with rheumatic heart disease 5 days after interruption of treatment for an appendectomy, coronary insufficiency in a patient 5 days after interruption for a tooth extraction, and transient cerebral vascular insufficiency in a patient 7 days after interruption of treatment because it was thought that the anticoagulant preparation might be producing a syndrome of dry mouth. From the observations in groups B and C it appeared that interruption of treatment for short periods of time could be accomplished without a great risk. Because of its different composition group C was dropped from further considera-

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Table 2

Differences in Mortality and Total Complication Rates of Groups A and B by Months of Exposure*

Month	Mortality rate					Total complication rate				
	Group A	Group B	Difference	SE of difference	Critical ratio	Group A	Group B	SE of Difference	SE of difference	Critical ratio
1	.219	0	.219	.0972	2.26	.406	.022	.384	.139	2.65
2	.154	.027	.127	.153	.8	.231	.027	.204	.209	.98
3	0	.029	.029	.156	.2	0	.029	.029	.299	.01

*Mortality rate was calculated as the ratio $\frac{d_x}{O_x - \frac{1}{2}W_x}$ in which d_x = the number of deaths, O_x the number of cases exposed to the risk, and W_x = the number of cases withdrawn from observation because of loss to follow up. Those who resumed treatment during the month were subtracted from O_x of the subsequent month. The total complication rate was calculated in the same way except d_x = sum of the number of fatal plus the number of nonfatal complications. The standard error was calculated by the formula $SE = \sqrt{\sum \frac{d_x}{O'_x\,(O'_x - d_x)}}$ in which $O'_x = O_x - \frac{1}{2}W_x$ and SE of difference $= \sqrt{\sum SE^2}$ Critical ratio $= \frac{\text{difference}}{SE}$

tion and comparisons between groups A and B only were made.

The high incidence of complications occurring shortly after interruption because of bleeding suggested a real difference in this group (fig. 1). This was even more evident when the period of exposure was taken into account. Since the patients in group B were withdrawn permanently they were continuously exposed to a risk. On the other hand, in group A many of the patients were started on treatment again as soon as the bleeding problem was controlled. From the formula[12] for calculating rates of survival and for survival without a complication for each month of exposure, it was observed that the difference in the mortality in the first month between group A and group B was sufficiently great to give a critical ratio of difference to standard error of 2.26 (p less than 0.05). If the same was calculated for both fatal and nonfatal complications, the critical ratio was 2.65 (p less than 0.01). After the first month there was no significant difference between the two groups (table 2).

The possibility was considered that a difference in the composition of the two groups might account for the results. It might be expected that the slight predominance of men in group A could bias this group toward an increased number of complications. It does not explain, however, why these should come any sooner. Moreover, group B was biased by having more patients with coronary artery disease in whom the chance of complication was greater and the prognosis consequently worse.

It is suggested that discontinuance of treatment early in the course of long-term anticoagulation might be accompanied by a higher complication rate than late discontinuance.[1] The possibility that patients in group A interrupted treatment earlier than those in group B was examined. The results indicated to the contrary that patients in group A had been on treatment slightly longer than those in group B before interruption. Those who had complications showed the same duration of treatment as those who did not. This applied in both groups (table 3).

Since differences in the composition of the groups did not seem to explain adequately the early appearance of complications in group A, other explanations were sought. Administration of vitamin K_1 might induce a return to a hypercoagulable state. Transfusions with banked blood might introduce thromboplastic substances analogous to the clot-promoting property of serum described by Wessler.[13] Tissue ischemia secondary to blood loss might

Table 3

Duration of Treatment before Interruption

		Number of cases	Duration of treatment before interruption: Mean (months)	Range (months)
Group A	Uncomplicated	25	7	1-48
	Complicated*	20	6	1-30
	Complicated within 4 weeks*	14	7	1-24
Group B	Uncomplicated	38	4	1-36
	Complicated*	15	4	1-40

*Refers to all thromboembolic complications, fatal and nonfatal.

initiate a series of events culminating in a thrombus formation. The role of these three factors was observed by comparison of complicated and uncomplicated patients in group A. There is some tendency toward complications in those who had ischemic symptoms such as chest pain or transient cerebral symptoms, as may be seen in table 4, but the numbers are too small to be of significance. There is no clear indication that vitamin K_1 or transfusions should be withheld for fear of precipitating a thrombotic complication. There is overlap in the figures given because a single patient often fell into more than one category.

The complications showed no definite relation to the source of the bleeding (table 5). Even after relatively minor bleeding such as hematuria and a small hematoma, fatal complications were observed. The presence of associated conditions such as ulcer or diabetes was not associated with an observable difference in rate of complications, but the figures are too small to be of significance.

Discussion

Two possible conclusions seem to be justifiable from the observations. First, a hypercoagulable state is induced as a direct result of the bleeding by a mechanism that is not clear. Second, a common factor might induce both the bleeding and the complication. It is possible, for instance, that a patient who is deteriorating might become sensitive to the anticoagulant and start bleeding. Since there were no differences in the composition of the groups, the latter hypothesis does not seem likely, and we are inclined to favor the first.

Table 4

Group A Relation of Three Factors to Presence of Complications

	Vitamin K_1	Transfusions	Ischemia	Total
Complicated*	12	6	5	20
Uncomplicated	13	5	1	25

*Refers to all thromboembolic complications, fatal and nonfatal.

Table 5

Group A. Type of Bleeding in Relation to Complications

Type of bleeding	Number of instances	Complicated*
Hematuria	12	7
Gastrointestinal	20	10
Epistaxis	3	0
Hematoma	2	1
Hemarthrosis	2	0
Other	6	2
Total	45	20

*Refers to all thromboembolic complications, fatal and nonfatal.

Whatever the mechanism, the results strongly point out that bleeding is a more undesirable complication than has generally been appreciated. To the risk of inducing a fatality as a direct result of bleeding there is added the more subtle risk of inducing a rebound complication that may be fatal. There are sufficient reports to indicate that the general incidence of a fatal bleeding episode during long-term anticoagulation is somewhere in the neighborhood of 1 per cent. The incidence of bleeding is around 10 per cent. If one assumes a bleeding rate of 10 per cent in patients on long-term treatment and a rebound (1 month) fatality rate of 16 per cent (seven out of 45 instances), then there could be expected to be 1.6 per cent greater mortality rate, making a total mortality rate of about 2.6 per cent. This is a figure comparable to that of many surgical operations and should instill further caution in the use of anticoagulants. Furthermore, reports that compare the future of patients who continue treatment with those who stop treatment because of bleeding are introducing a bias.

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Summary

From a series of 310 patients on long-term anticoagulant treatment for various conditions 136 instances were collected in which treatment was interrupted. This was because of bleeding in 45 instances, for permanent reasons in 53 instances, and for temporary reasons in 38 instances.

Rebound thromboembolic complications were observed significantly more frequently in those who stopped treatment for bleeding. The cause of the rebound effect could not be ascribed to vitamin K_1 administration, transfusions, or overt ischemic effects from blood loss although the latter might have been contributory to a small extent. The observations suggested a hypercoagulable state induced directly in some obscure way as a result of the bleeding.

Interruption of treatment for reasons other than bleeding was not associated with early complications. The risk of interruption of treatment for short periods was relatively small (three nonfatal complications in 38 instances). In those who stopped permanently, complications were most often seen after 2 months.

Acknowledgment

We wish to express our appreciation to Dr. Hugo Muench for assistance in the statistical procedures.

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Hemodynamic Studies in Pectus Excavatum

By CLIFFORD S. REUSCH, CAPT. USA MC

THE PRESENCE of abnormal cardiac auscultatory findings of no diagnostic significance in pectus excavatum (funnel chest) has been repeatedly emphasized.[1] However, published hemodynamic data in this condition are limited to 42 cases.[2-8] It is the purpose of this paper to report eight additional cases with cardiac catheterizations that originally were diagnosed as organic heart disease.

Method of Study

The patients reported in this series were seen as routine referrals to the cardiac clinic of the City of Hope Medical Center during the course of one calendar year. In each instance, the patient was thought by his referring physician to have organic heart disease.

In addition to routine 14-lead electrocardiograms, each patient had a vectoreardiogram made with 3-lead systems (Kimura, Grishman, and Frank), a phonocardiogram,* and a cardiac fluoroscopic examination.

Cardiac catheterization was performed on each patient. An Electronics-for-Medicine multichannel photographic recorder† was employed for a permanent pressure record. Oxygen saturation data were recorded on Enseo and Waters indirect oximeters, and were checked at intervals during the procedure with Van Slyke gasometric determinations. Five minutes of exercise on a bicycle ergometer at the rate of 30 ergs per minute was carried out in most instances.

In each case dye-dilution curves were obtained with multiple injection sites throughout the right heart and recorded by continuous sampling from the radial artery. Indocyanine green was the dye indicator employed. Cardiac output was determined by the method of Fick,[9] as well as from the dye indicator-dilution curves with the method of Hamilton[10] and Stewart[11] et al. Cardiac index was calculated from the cardiac output derived by the Fick principle. Total peripheral resistance (TPR) was calculated by the formula:

$$TPR = \frac{\text{mean arterial pressure} \times 1332 \times 60}{\text{cardiac output ml./min.}}$$

Selective angiocardiograms were made in two cases.

In all instances the cardiac catheterization was performed under local anesthesia, with hydroxyzine or a combination of secobarbitol, promethazine hydrochloride, and codeine as premedication.

Case Reports

Case 1

A 25-year-old Caucasian woman without symptoms was examined because of a murmur first discovered at the age of 5 years. Her blood pressure was 125/76, pulse rate was 82. A mild pectus excavatum was largely obscured by breast tissue. The chest was normal to auscultation and percussion. On cardiac examination the aortic second sound equaled the pulmonary second sound. A grade-III systolic murmur was heard at the second and third left intercostal spaces; a grade-IV systolic murmur was heard at the apex. A thrill was also felt at the apex. The tentative diagnosis was mitral insufficiency.

Case 2

A 32-year-old Caucasian man was examined because of palpitations and dizziness. He had a history of murmur present from age 12 years. The blood pressure was 180/90, the pulse was 90 and regular. The chest was normal to auscultation and percussion. There was a moderate pectus excavatum of the anterior chest. On cardiac examination the point of maximum impulse was in the fifth intercostal space at the midclavicular line. The pulmonary second sound was equal in intensity to the aortic second sound and closely split. In the sitting position, there was a grade-III systolic murmur at the apex, and a thrill was present. In the recumbent position, the apical murmur was grade I in intensity, and the thrill was absent. The tentative diagnosis was mitral insufficiency.

Case 3

A 3-year-old Caucasian boy was examined because of easy fatigue on exertion. A murmur was known to be present since the age of 6 weeks. Blood pressure was 75/50, and the pulse was 100 and regular. The chest was normal to auscultation and percussion. There was a mild pectus

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*Sanborn Twin-beam Stethographic Recorder (Model 62)

†Electronics for Medicine, Model DR8 Research Recorder, 17 South Lexington Avenue, White Plains, New York.

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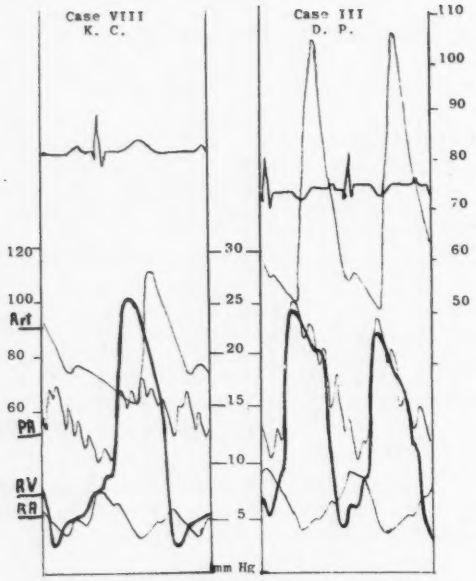

Figure 1

Superimposed presssure tracings (redrawn) on Cases 8 and 3. The center calibration column indicates right heart pressure in both cases. Outside calibration columns indicate arterial pressures. The time interval is one second.

excavatum. On cardiac examination the point of maximum impulse was in the fifth intercostal space, 1 cm. to the left of the midclavicular line. The pulmonary second sound was equal in intensity to the aortic second sound and closely split. There was a grade IV systolic murmur at the fourth left intercostal space, and a thrill was present in this area. The tentative diagnosis was interventricular septal defect.

Case 4

A 6-year-old Caucasian boy without symptoms was examined because of a murmur known to have been present since age 3 months. The blood pressure was 100/65, the pulse was 90 and regular. Auscultation and percussion of the chest were normal, and a moderate pectus excavatum was present. On cardiac examination the point of maximum impulse was in the fifth intercostal space at the midclavicular line. The pulmonary second sound was equal in intensity to the aortic second sound and closely split at the pulmonary area. There was a grade-IV high-pitched blowing systolic murmur at the fourth left intercostal space. A thrill was present in the left fourth intercostal space. The tentative diagnosis was interventricular septal defect versus an interatrial septal defect.

Case 5

An 8-year-old Caucasian girl was examined because of frequent upper respiratory infections and a murmur known to have been present since age 6 months. The blood pressure was 110/70, the pulse was 88 and regular. Auscultation and percussion of the chest were normal. There was a mild pectus excavatum deformity of the anterior chest. On cardiac examination the pulmonary second sound was equal in intensity to the aortic second sound and closely split in the pulmonary area. There was a grade-III systolic murmur at the fourth left intercostal space, which was referred to the apex and the aortic area. An indefinite thrill was also present in the fourth left intercostal space. The tentative diagnosis was interventricular septal defect.

Case 6

A 32-year-old Caucasian woman was examined because of fatigability and a murmur discovered 3 months previously during psychiatric hospitalization. The blood pressure was 120/70, the pulse was 70 and regular. Auscultation and percussion of the chest were normal; there was a pectus excavatum deformity of the anterior chest obscured by breast tissue. On cardiac examination the point of maximum impulse was in the fifth intercostal space at the midclavicular line. The pulmonary second sound was equal in intensity to the aortic second sound. There was a grade-III systolic murmur at the third left intercostal space. No thrill was present. The tentative diagnosis was interatrial septal defect.

Case 7

A 20-year-old Caucasian man without symptoms was examined because of a murmur discovered on military pre-induction physical examination. Blood pressure was 116/80, the pulse was 82 and regular. Auscultation and percussion of the chest were normal. There was a mild pectus excavatum deformity of the anterior chest wall. On cardiac examination the point of maximum impulse was in the fifth intercostal space at the midclavicular line. The pulmonary second sound was equal in intensity to the aortic second sound and widely split in both areas. There were a grade-III systolic murmur and a thrill at the fourth left intercostal space. A variable third heart sound was heard at the fourth intercostal space. The tentative diagnosis was interatrial septal defect.

Case 8

A 12-year-old Caucasian boy without symptoms was seen for the evaluation of a murmur known to be present since the age of 11 years. The blood pressure was 100/65, the pulse was 86 and regular. Auscultation and percussion of the chest were normal. There was a moderate pectus excavatum

Table 1

Hemodynamic Data from Cardiac Catheterizations Performed on Eight Patients with Pectus Excavatum

Case Patient	I M.V.S.	II R.S.	III D.P.	IV D.W.	V S.S.	VI S.H.	VII W.M.	VIII K.C.
Age	25	32	3	6	8	32	20	12
Right atrial mean pressure	5	7	8	4	3	5	5	4
Right ventricular pressure	33/4	17/5	24/2	27/0	35/2	23/2	21/3	28/3
Right ventricular end-diastolic pressure	8	7	6	4	6	4	5	8
Pulmonary artery pressure	33/14	18/12	26/14	27/10	35/15	18/6	21/10	17/8
Pulmonary artery mean pressure	20	14	20	17	22	13	14	13
Pulmonary wedge pressure	16/10	Not Obt	Not Obt	13/8	9/7	12/5	9/7	13/8
Peripheral arterial pressure	120/65	110/66	102/48	117/60	123/70	115/63	130/70	120/68
Cardiac output ml./min.	5,600	7,500	6,100	2,800	4,700	3,200	4,500	7,600
Cardiac index L./min./M.^{2}	3.4	3.6	8.5	3.4	4.5	2.0	2.7	5.6
Peripheral resistance	1,270	846	864	2,100	1,680	2,000	1,670	860
Total pulmonary resistance	286	148	184	480	332	250	252	147

deformity of the lower sternum with a "flat chest." On cardiac examination the point of maximum impulse was in the fifth intercostal space at the midclavicular line. The pulmonary second sound was split and greater in intensity than the aortic second sound. There were a grade-IV systolic murmur and a thrill present in the second and third left intercostal space. The tentative diagnosis was mitral insufficiency.

Results

The hemodynamic data are summarized in table 1. Superimposed pressure tracings obtained at the time of cardiac catheterization are presented in two cases in which minor abnormalities were found (fig. 1). Phonocardiograms and right precordial electrocardiographic leads are shown for all cases (fig. 2). Vectorcardiograms of four of these cases are presented (fig. 3). A photograph of case 8 (fig. 4) demonstrates a "moderate" degree of pectus excavatum.

The hemodynamic data of our eight cases are not grossly abnormal. In case 3 there was a mild diastolic gradient across the tricuspid valve, which was associated with an abnormally high cardiac index and resting cardiac output. This small gradient across the tricuspid valve may come from the increased flow rather than a direct effect from the pectus excavatum. In two cases there was a small gradient across the pulmonic valve, 11 mm. of mercury in one case, and 5 mm. in the other. Again, in the first of these two, there were a relatively large cardiac output and cardiac index. This finding is not at variance with previously reported transpulmonic gradients in normal individuals, especially with slight increases of cardiac output.[12] Dye-dilution curves were normal in all cases.

In cases 1, 2, and 6 exercise was performed during the cardiac catheterization. In the first two, there was a substantial increase in cardiac output with a resultant drop in the pulmonary and systemic resistances, and no essential change in the intracardiac pressures. In case 6 cardiac output determinations were

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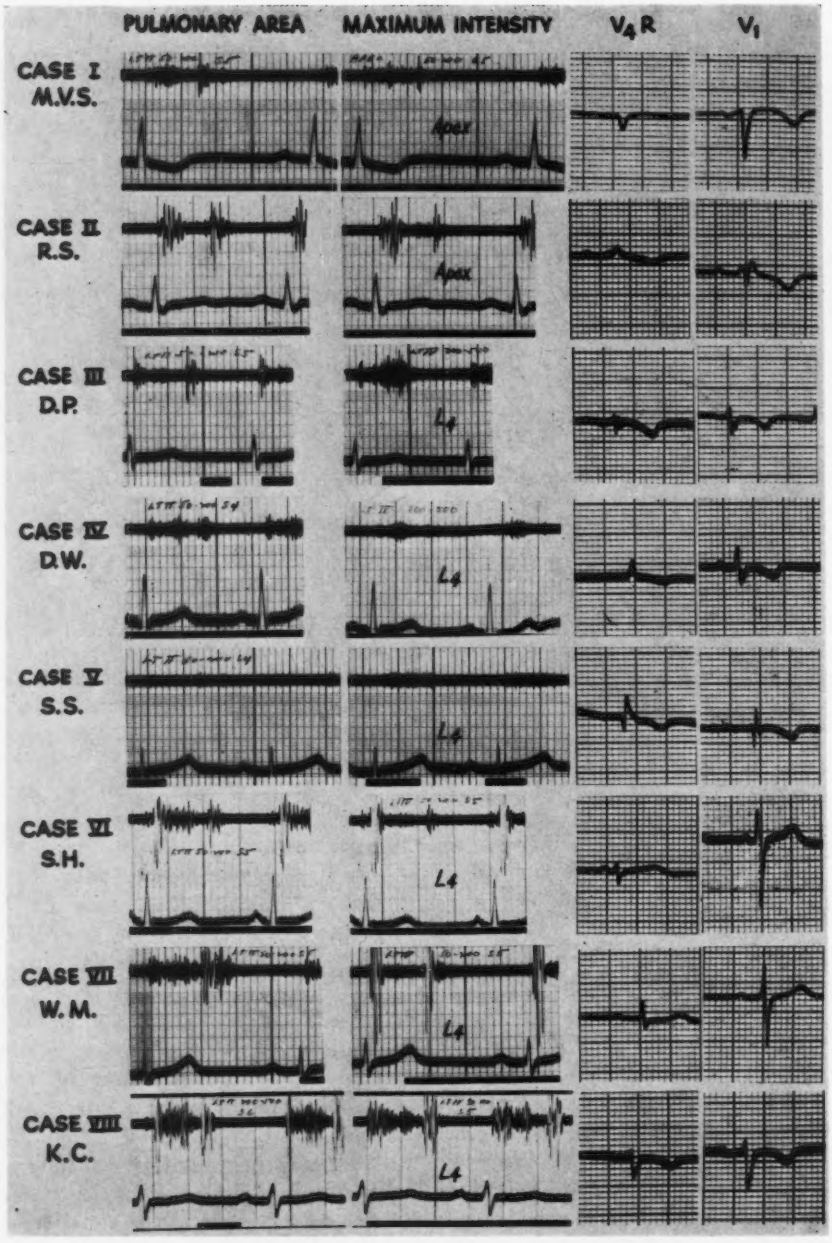

Figure 2

Phonocardiograms and right precordial electrocardiograms on all cases.

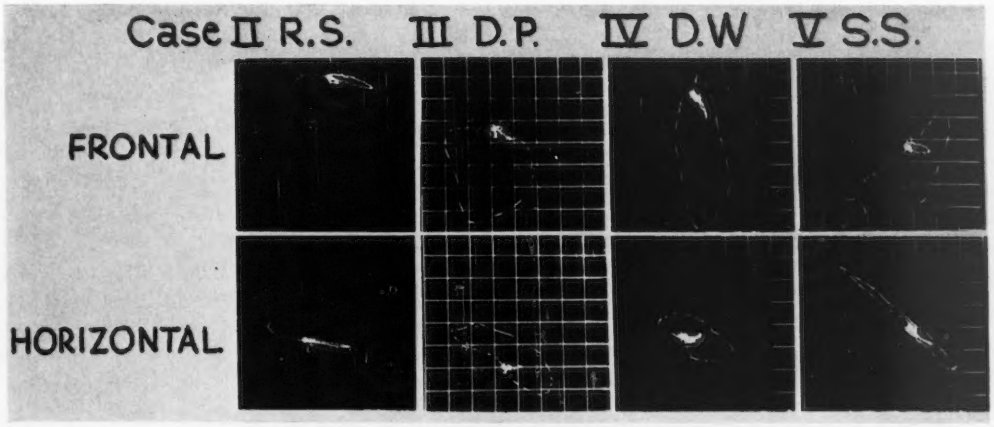

Figure 3

Frontal and horizontal vectorcardiograms (Kimura lead system). All frontal depolarization progresses in a clockwise direction. All horizontal depolarization is counterclockwise.

not made during exercise. However, pressure relationships remained normal. In addition, case 1 had a left heart catheterization that failed to reveal any abnormality.

Discussion

The incidence of pectus excavatum in the population as a whole is not low. Lang[13] reported its occurrence in 2.2 per cent of boys and a 2.5 per cent of girls in a series of German school children.

Schaub and Wegmann,[1] in a review of 137 cases of pectus excavatum, found cardiac auscultatory abnormalities in 57 per cent. Systolic murmurs were heard in 33 per cent, and the remainder had splitting of heart sounds or third heart sounds. In reported cases with hemodynamic data, the point has been re-emphasized that the evaluation of auscultatory findings in the presence of a pectus excavatum must be carried out with great caution. In addition to the previously described benign findings of splitting of the second sound and parasternal systolic murmurs, six of the present cases had a slight systolic thrill.

The presence of a benign thrill has not been mentioned previously among the diagnostic peculiarities of pectus excavatum in the absence of hemodynamically significant cardiac disease. This is of relatively great importance, as the presence of a thrill is usually considered a diagnostic sign par excellence of organic heart disease.[14, 15]

The electrocardiographic abnormalities in pectus excavatum are relatively constant. Dressler and Roesler[16] pointed out that there is a persistence of the juvenile pattern with inversion of the T waves across the right-sided precordial leads. Incomplete right bundle-branch block and right axis shift or deviation are also common.[17] Both persistent juvenile pattern and incomplete right bundle-branch block occur in the absence of any discernible abnormality, however, and may be normal variants.[18, 19]

In the past, much of this electrical pattern has been attributed to physical change produced by pressure of the sternum against the right ventricle. The vectorcardiographic evidence presented by Wachtel, Ravitch, and Grishman,[2] as well as our own tracings, indicates that the abnormalities are more likely on the basis of a displacement of the heart toward the left. A relative difference in position of the precordial electrode on the deformed precordium in relationship to the cardiac vectors, rather than a rotation of the heart, per se, results in the pattern described.

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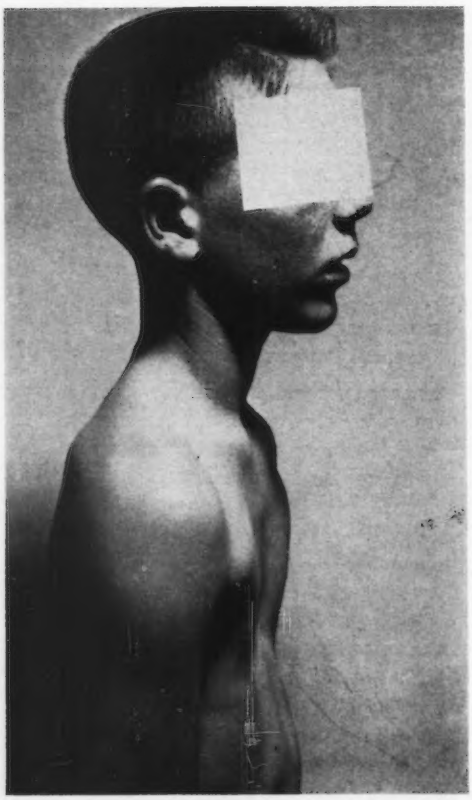

Figure 4

Lateral photograph of case 8 demonstrating a moderate degree of pectus excavatum.

Of interest regarding the electrocardiographic changes seen in pectus excavatum was the disappearance of the incomplete right bundle-branch block in 62 per cent of the cases following surgery.[20]

The radiographic findings are proportional to the displacement of the sternum posteriorly. The findings consist of leftward displacement of the cardiac shadow and increasing prominence of the pulmonary artery segment.[21] On occasion, the obliteration of the retrosternal free space may be erroneously attributed to right ventricular hypertrophy, as it was initially in three of our own cases. The lateral radiogram may be most helpful, as it was in one of our female patients in whom the minimal pectus deformity was obscured by an ample amount of breast tissue. In this instance, the slight deviation of the lower sternum posteriorly was recognized only at the time of lateral chest films.

Physicians in general practice often have an opportunity to witness the familial characteristics of this condition. In most of the cases presented here other members of the family were examined. In one instance three members of the same family had a pectus excavatum. One patient described both his father and grandfather as having similar chest contours. A family studied by Elisberg[22] demonstrated 50 per cent transmissability through four generations.

Currently 42 cases of pectus excavatum have been reported with hemodynamic data.[2-8] Four of these cases had congenital heart disease in addition to pectus excavatum; all four cases were reported by Fabricius et al.[4] In six of the remaining 38 catheterized patients with pectus excavatum, minor abnormalities were found. In three cases, small systolic gradients were found across the pulmonic valve, similar to those mentioned by Callahan et al.[12] in normal individuals. In two instances, there were elevation of the end-diastolic pressure in the right ventricle and an abnormal diastolic pressure curve, similar to that seen in constrictive pericarditis. In four instances, there was some elevation of mean atrial pressure with a pressure gradient between the right atrium and right ventricle.

Respiratory abnormalities associated with pectus excavatum have been mentioned on several occasions, the most extensive study being that by Brown and Cook.[23] They consistently found a reduction of the maximum breathing capacity and increased residual volume, while other measures of pulmonary function remained within normal limits.

McKusick,[24] who emphasized the importance of pectus excavatum in the Marfan syndrome, pointed out that several cases of cardiac disease seen with pectus excavatum have subsequently been found to have the Marfan syndrome. He also noted that a diastolic murmur has not been reported as part

of the auscultatory abnormality in pectus excavatum and, when present, indicates a need for vigorous cardiac evaluation.

How a pectus excavatum deformity of the anterior chest wall is produced remains in question. The histologic studies of Chin[25] have fortified Brodkin's original hypothesis that this represents a developmental abnormality of the anterior portion of the diaphragm. Their work is entirely compatible with the observed congenital and hereditary nature of the defect and stands as the most attractive evidence in favor of this hypothesis.

In addition to the obscure etiology of this condition, the genesis of the symptomatology also remains in question. On the basis of clinical evidence, pectus excavatum has been implicated in the production of congestive heart failure and severe cardiac embarrassment. This assumption has not been supported by hemodynamic data. In one of the cases reported by Wachtel et al.,[2] cardiac output was reduced after exercise. Observations made on angiography by Howard[26] tend to show some encroachment on the right ventricular cavity by the depressed sternum. These findings, however, are isolated and limited to severe deformities. In angiocardiograms performed on two of the patients in the current series, no reduction of the right ventricular chamber by compression between the left ventricle and anterior chest wall was demonstrated.

In the eight cases presented here, little in the way of symptomatology needs to be discussed, but the dramatic auscultatory findings do require explanation. Inasmuch as pulmonary systolic murmurs have been reported in thin individuals with no abnormal hemodynamic findings, it would appear that reducing the space between the pulmonary artery and the auscultating device would intensify these sounds. If the pulmonary artery segment or outflow track of the right ventricle were in apposition with the anterior chest wall, the observed thrill might result. This may be considered an exaggeration of a normal occurrence rather than an obscure pathologic mechanism.

Conclusions and Summary

Eight cases of mild to moderate pectus excavatum have been reviewed. Electrocardiographic and phonocardiographic tracings, hemodynamic data obtained from cardiac catheterization, and physical findings are presented. All eight individuals are considered to have a normal hemodynamic pattern despite the fact that auscultatory findings had led to a presumptive diagnosis of organic heart disease. A brief discussion of the incidence and significance of pectus excavatum is presented with reference to the available published hemodynamic data.

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It is with the symptoms of disease that the patient, and that the doctor mainly, contends; and the symptoms of heart disease may be said to derive almost exclusively from faults in function. Therefore, in managing our patients, our thoughts must be chiefly set in terms of function and not of structure. To whom I fail to teach this first simple, but essential, lesson I have nought to teach.—Sir Thomas Lewis. *Diseases of the Heart.* New York, The MacMillan Company, 1933, p. vii.

Reticulocytosis and Hypoxemia as Prognostic Signs in Congestive Heart Failure

By JOHN THOMAS, M.D., OTIS MICHAEL, B.S., AND CLEVE W. EWELL, M.D.

THE APPEARANCE of immature red blood cells in the peripheral blood of patients with congestive heart failure has been well documented in the literature.[1-4] Frumin and colleagues[1] reported that nucleated red cells found in the blood of patients in congestive heart failure indicated a poor prognosis and attributed this to anoxemia resulting from the cardiac decompensation. Groen and Godfried[2] suggested that normoblasts found in patients with cardiac disease signified massive pulmonary infarction. These reports emphasized the presence of nucleated red blood cells, or normoblasts, in the peripheral blood as an unfavorable prognostic sign in patients with cardiac insufficiency. The purpose of this study is to observe this phenomenon further, and to determine if reticulocyte counts may be used to reflect the degree of arterial oxygen unsaturation and thus serve as a prognostic sign in congestive heart failure.

Method

The study is composed of observations on 15 patients with severe congestive heart failure* who were admitted to the medical service of George W. Hubbard Hospital of Meharry Medical College. The etiology of the heart disease was distributed as follows: hypertensive and arteriosclerotic, 10; arteriosclerotic without hypertension, three; syphilitic and rheumatic, one each. Venous pressure, circulation time, and nonprotein nitrogen were recorded on each subject. Arterial blood was collected from the femoral or brachial artery in oiled heparinized syringes and capped immediately. Oxygen determinations were performed in the Van Slyke manometer. None of the patients had received oxygen less than 12 hours before the sample was obtained. Venous blood was drawn at the same time for the hematologic studies. Serial red blood cell and reticulocyte counts, hemoglobin, and hematocrit determinations were performed on all subjects.

Results

Within 1 month after admission, five of the 15 subjects died. There was no demonstrable clinical difference between the deceased and the now living subjects, and some of the deceased patients had a better clinical prognosis than did those in the latter group. All of the patients who died had a reticulocyte count greater than 3.0 per cent, the range being 3.0 to 4.9 per cent, with an average of 4.0 per cent. On the other hand, the 10 patients that improved, and are now living, had a reticulocyte count less than 2.2 per cent, with an average of 1.5 per cent. These findings are significant at the .001 level according to the t-test for difference between means.

In all patients except one, the arterial oxygen saturation was reduced; the average of these findings indicates a reciprocal relationship between the degree of hypoxemia and the reticulocytosis (table 1). The average arterial oxygen saturation of the five deceased patients was 83 per cent as compared to an average of 88 per cent in the patients that survived. This, however, was not a statistically significant difference. Two of the five patients that died had nucleated red cells in the peripheral blood. In all cases except one, the nonprotein nitrogen was slightly elevated but none of the patients was uremic. The white blood cell and differential counts were normal in all subjects.

Case five is particularly interesting in that serial oxygen and reticulocyte determinations were obtained (fig. 1). The patient was

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*Functional capacity Class IV and therapeutic Class E, Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels by the Criteria Committee of the New York Heart Association, Inc., 1953.

Table 1

Peripheral Blood Analysis of 15 Patients in Congestive Failure

Case no.		Venous pressure ml. water	Circulation time, sec.	WBC cells/mm.³	RBC cells/mm.³ X 10⁶	Hemoglobin Gm. %	Hematocrit vol. %	Reticulocytes %	Nucleated red cells/100 WBC	O₂ sat. %	Nonprotein nitrogen mg. %
1	Dead	300	65	7,600	5.54	17.0	49	3.0	1	86	59
2	Dead	280	40	8,500	4.84	15.0	46	3.1	0	81	62
3	Dead	295	30	7,350	4.31	12.5	38	4.5	1	88	30
4	Dead	285	55	4,600	4.33	14.5	39	4.9	0		78
5	8/26/60	250	60	7,100	3.94	12.0	36	1.1	0	90	49
	Dead 9/12/60	190	75	5,800	3.65	11.5	36	2.1	0	86	55
	9/13/60			5,750	3.20	12.0	38	4.4	0	76	41
6	Alive	210	50	7,150	5.55	16.5	48	1.9	0	88	38
7	Alive	290	35	9,950	5.68	18.5	61	2.2	0	89	49
8	Alive	265	35	10,550	3.96	13.0	37	1.4	0	81	68
9	Alive	270	47	5,100		17.0	48	1.2	0	91	43
10	Alive	200	40	8,700	5.44	19.0	52	1.2	0	86	36
11	Alive	280	35	7,050	4.44	13.5	38	2.1	0	82	84
12	Alive	245	40	6,000		16.5	49	1.2	0	90	54
13	Alive			12,500	3.84	11.5	36	1.3	0	78	36
14	Alive	115	42	4,750	4.10	11.5	35	1.3	0	96	55
15	Alive	280	40	8,000	4.44	15.0	43	0.9	0	98	40

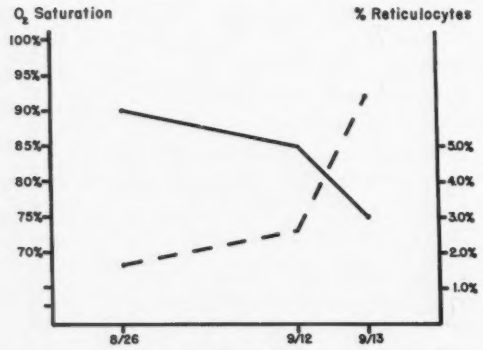

Figure 1

Relationship of reticulocytosis and hypoxemia in case 5. Solid line, oxygen saturation; broken line, reticulocytes.

a 50-year-old man with aortic insufficiency due to syphilis and, in addition, portal cirrhosis. The outstanding findings on physical examination were distended neck veins, jaundice, moist rales in both lung fields, aortic diastolic murmur, hepatomegaly, and marked ascites. At the time of admission dyspnea was not a prominent symptom. The reticulocyte count was 0.9 per cent and arterial oxygen saturation was 90 per cent on admission. After 2 weeks of hospitalization he became increasingly more dyspneic and the jaundice increased. The reticulocyte count was elevated to 2.4 per cent and the arterial oxygen saturation decreased to 86 per cent. After 2 days the reticulocyte count increased to 4.9 per cent and the arterial oxygen saturation decreased to 76 per cent. He died the following day.

Discussion

These studies emphasize the importance of reticulocytes and other immature forms of red blood cells in the peripheral blood of patients with congestive heart failure. Groen and Godfried[2] attributed the appearance of normoblasts to anoxia related to massive pulmonary infarcts or mural thrombi. Such a relationship was not established in this study. The observations here correlate with the findings of Waller, Blumgart, and Volk,[3] who noted increased red cell fragility and reticulocytosis in patients with pronounced congestive heart failure. These findings were attributed to stasis and anoxemia.

Nucleated red cells were found in the blood of only two of the five patients who died, whereas reticulocyte counts above 3.0 per cent were found in all patients who died. Although four of the patients had mild anemia, there was a good correlation between the reticulocyte count and the arterial oxygen saturation. The direct bilirubin of case 5 was increased, as a result of long-standing portal cirrhosis with superimposed congestive heart failure. The correlation of arterial oxygen saturation with the appearance of immature red blood cells in the peripheral blood of patients in congestive heart failure has not, to the knowledge of the writers, been previously reported.

Conclusions

Reticulocytosis and nucleated red cells in the peripheral blood of patients with congestive heart failure suggest an unfavorable prognosis.

The arterial oxygen saturation was decreased in all patients studied except one.

The findings suggest that a rise in the reticulocyte count in patients with congestive heart failure suggests a grave prognosis, and is a more useful tool than the nucleated red cell count.

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Religio Medici

For my Religion, though there be several Circumstances that might perswade the World I have none at all, (as the general scandal of my Profession, the natural course of my Studies, the indifferency of my Behaviour and Discourse in matters of Religion, neither violently Defending one, nor with that common ardour and contention Opposing another;) yet, in despight hereof, I dare without usurpation assume the honourable Stile of a Christian.—Sir Thomas Browne. *Religio Medici,* 1642, edited by W. A. Greenhill, M.D., Oxon., London, MacMillan and Co., Limited, 1950, p. 7.

Some Unusual Features of the Marfan Syndrome

Report of Four Cases

By NAIP TUNA, M.D., AND ALAN P. THAL, M.D.

IT IS generally agreed that the Marfan syndrome is a heritable disorder of connective tissue characterized by widespread malformations affecting the musculoskeletal, cardiovascular, and ocular systems. It was first described by Marfan in 1896 under the name of dolichosténomélie.[1] In 1902 Archard presented a case and called the syndrome arachnodactyly.[2] Thus, the musculoskeletal malformations were initially described in this syndrome. Later, attention was drawn to the frequency of associated cardiovascular and ocular abnormalities, particularly ectopia lentis. Other malformations have also been reported such as susceptibility to respiratory infections, developmental malformations of the lung, cystic disease of the lung, and spontaneous pneumothorax. Several reviews covering different aspects of this syndrome have been published.[3-5] The purpose of this paper is to present some unusual findings in four patients with the Marfan syndrome.

Case Reports

Case 1

C. W. UH no. 652585, a 33-year-old white man, was admitted to the University of Minnesota Hospitals because of stiffness and pain in the knees and shortness of breath of 6 months' duration and progressive loss of vision due to subluxation of lenses since early childhood. Six years prior to admission he noted a hard mass in the left side of his neck close to the angle of the mandible. Three years prior to admission he noted a second mass in front of the previous one. Both masses progressively increased in size. Associated with the appearance of masses in the neck the patient noted dizzy spells lasting from a few seconds to a minute. There was no family history of ocular abnormalities or skeletal changes.

Physical examination revealed a slender young male who was comfortable at rest. The blood pressure was 102/60 mm. Hg. The height and the span were 71 3/4″ and 72 1/4″ respectively. Both lenses were dislocated. The vision on the right side was 20/200 and on the left side 10/400 (with glasses). The palatal arch was high. There was a mass about 3 by 2 by 3 cm. underlying the left jaw in the midcervical region laterally and a second mass, posterior to the left sternocleidomastoid muscle, which was firm and ovoid and about the same size. A moderate degree of pectus excavatum was present. The heart was not enlarged. The aortic second sound was louder than the pulmonic and there was a grade III (graded I-VI) aortic diastolic murmur, best heard along the left sternal border and the third and fourth intercostal spaces. He had typical arachnodactyly. There was some stiffness of the knees with minimal limitation in the range of motion. The hemoglobin, leukocyte count, leukocyte differential count, urinalysis, and serum proteins were normal, and the serology was negative. The electrocardiogram showed high QRS voltages compatible with left ventricular hypertrophy. Chest film showed normal heart silhouette (fig. 1). Cardiac fluoroscopy demonstrated increased pulsations of the left ventricle, ascending aorta, and aortic arch. X-rays of the neck revealed a soft tissue mass in the left side of the neck with a smooth outer contour. X-rays of the knees showed marked subchondral sclerosis with no significant decrease in the joint spaces. There was also some osteoporosis, and a loose body in the left knee. Retrograde aortogram done after injection of 50 ml. of 90 per cent hypaque through a catheter in the sinus of Valsalva area showed marked aneurysmal dilatation of the sinus of Valsalva and of the ascending aorta about the sinus of Valsalva (fig. 2). The anteroposterior diameter of the sinus area measured approximately 10 cm. There was distinct aortic regurgitation as well. The distal half of the ascending aorta and the remainder of the thoracic aorta were not remarkable. Simul-

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Figure 1

Case 1. Posteroanterior and oblique chest films.

taneous carotid angiogram showed an extensive network of small vessels, indicating a tumor mass adjacent to the left carotid bifurcation (fig. 3). Biopsy of the femoral artery was normal. On March 18, 1960, the patient was operated upon and a highly vascular, stony hard mass was removed from the bifurcation of the left carotid artery. There was a surrounding loose capsule, which was highly vascularized. A group of lymph nodes surrounded the internal carotid artery adjacent to the tumor. The histologic diagnosis was chemodectoma (carotid body tumor) (fig. 4), and benign hyperplasia of lymph nodes.

This 33-year-old patient has typical skeletal and ocular changes of the Marfan syndrome. Although the family history is negative, disease in other members of the family cannot be excluded definitely. There are two unusual features in this case: the occurrence of marked aneurysmal dilatation of the sinus of Valsalva area undetected in routine chest x-rays, and the occurrence of a carotid body tumor in association with the Marfan syndrome.

Case 2

G. M., UH no. 949620, a 19-year-old white male student, developed spontaneous pneumothorax in November 1959. In January 1960, he noticed precordial chest pain radiating to the left jaw and down to the left ulnar region, lasting 1 to 2 hours, on two occasions, while playing hockey. He had two operations for pectus excavatum in 1950 and 1956. No cardiac abnormality was noted at that time. His parents, two brothers, and two sisters are apparently healthy. An older sister and the mother wear glasses for myopia. Physical examination revealed a slender, tall man in no distress. His height, span, heel-to-pubis and vertex-to-pubis measurements were 76 1/2, 81, 41 1/4, and 35 inches respectively. The blood pressure was 104/58 mm. Hg and equal in both arms. He had arachnodactyly, high arched palate, hammer toes, dorsal scoliosis, and partially corrected pectus excavatum. There was a grade-IV blowing diastolic murmur best heard over the aortic area and third intercostal space, left sternal border. The heart was not enlarged. Urinalysis, hemoglobin, leukocyte count, leukocyte differential count, electrocardiogram, and cardiac fluoroscopy were all within normal limits. Except for pectus excavatum and dorsal scoliosis the chest x-rays were negative (fig. 5). Retrograde aortogram on February 18 showed a large aneurysm of the sinuses of Valsalva, dilatation of the aortic ring, large aortic cusps, and minimal aortic regurgitation (fig. 6). The coronary arteries appeared normal. Biopsy of the femoral artery was normal. When seen again in 1961 he complained of tiredness and frequent sharp pains in the precordium. In addition to the diastolic murmur noticed 1 year previously, there were grade-II apical and aortic systolic murmurs. On fluoroscopy the ascending aorta appeared slightly larger. The electrocardiogram was unchanged.

This case represents the typical Marfan syndrome, with skeletal, pulmonary (pneumothorax), and aortic involvement. It is of interest that cardiac fluoroscopy and routine chest films again

Figure 2

Case 1. Retrograde aortogram showing large aneurysm involving the root of the aorta and the sinuses of Valsalva. In addition there is a moderate degree of aortic regurgitation.

failed to reveal the large aneurysm involving the intrapericardial portion of the ascending aorta.

Case 3

R. G., UH no. 958838, a 22-year-old white man, was admitted to the University of Minnesota Hospitals on June 14, 1960, because of severe congestive heart failure. The patient was slender as a child and at age 10 developed shortness of breath on exertion, and required digitalis and mercurial diuretics. He had had moderate shortness of breath until May 1960, when his symptoms began to increase gradually. He developed marked edema and bilateral pleural effusion, and required frequent mercurial injections. In February 1960, he developed severe crushing precordial chest pain aggravated by coughing but without radiation. Twelve hours after the onset of pain the patient became totally aphonic for several days, with gradual return of full voice over a 2-week period. His father, brother, and sister were tall, slender persons with skeletal changes quite characteristic of the Marfan syndrome. The father had a grade-I pulmonic systolic murmur. No cardiac abnormalities were otherwise detected in the members of the family. On admission, he appeared chronically ill and in marked congestive heart failure. There was severe pectus excavatum, arachnodactyly, pes planus, bilateral subluxated lenses, and a high, narrow arched palate (fig. 7). His weight was 135½ pounds, the height 78 inches, and the span 83 inches. The blood pressure was 130/40 mm. Hg in the left arm, and 75/40 in the right arm. The pulse was regular, 108 per minute. The left carotid pulse was extremely weak; the right one was bouncing. There was marked cardiomegaly, and the left subclavian artery showed aneurysmal dilatation. A left atrial gallop was prominent at the apex. In addition, there were a harsh grade-II holosystolic murmur and a palpable systolic thrill in the third intercostal space, left parasternal area, and a grade-II blowing diastolic murmur heard best in the same area. The aortic second sound was greater than the pulmonic. The liver was 1½ fingerbreadths below the right costal margin. The right radial pulse was markedly diminished. There was also a spina bifida. Urinalysis, leukocyte count, hemoglobin, blood urea nitrogen, fasting blood sugar, serum electrolytes, and carbon dioxide combining power were all within normal limits. Cardiac fluoroscopy and chest roentgenograms revealed thoracic scoliosis, marked pectus excavatum, abnormally prominent aorta with increased pulsations both in the arch and in the ascending aorta, and increased pulmonary vascularity (fig. 8). Several blood cultures were negative. In spite of treatment, the patient's general condition rapidly deteriorated and he died on the fourth day of his hospitalization. Necropsy showed (1) dissecting aneurysm of the aorta with involvement of the carotid and subclavian arteries, (2) thrombosis of the left common carotid artery, (3) dilatation of the aortic ring, (4) severe, diffuse, cardiac dilatation involving both valve rings and cardiac chambers, (5) patent ductus arteriosus, (6) pulmonary emphysema, and (7) skeletal changes of the Marfan syndrome: high arched palate, tall, thin habitus, arachnodactyly, spina bifida, involving the ninth and tenth thoracic vertebrae, and pectus excavatum. The dissecting aneurysm starting from three intimal ruptures just distal to the aortic valve extended into the innominate, left common carotid, and left subclavian arteries and ruptured back into the aortic lumen, approximately 2 cm. distal to the origin of the left subclavian artery. There was a recent thrombus in the left common carotid artery extending up into the neck.

Microscopic examination of the left ventricular myocardium was normal. Sections from the aortic valve area, however, showed fragmentation and fatty infiltration of the myocardial fibers. The root of the aorta showed marked medionecrosis with disruption of elastic fibers. Sections from

Figure 3

Case 1. Pathologic vessels in and around chemodectoma at the left carotid bifurcation.

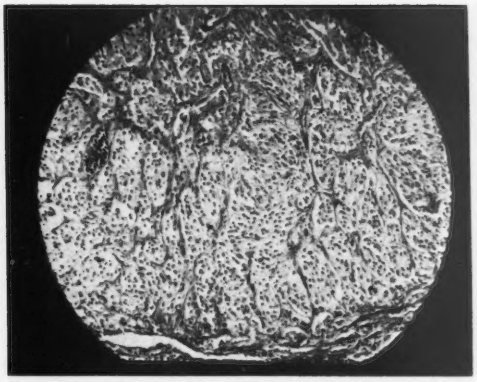

Figure 4

Case 1. Medium-power view of chemodectoma.

several levels of the aorta and the renal, splenic, both carotid, both femoral, and pulmonary arteries showed similar changes.

There was capillary telangiectasia of the brain and encephalomalacia resulting from the carotid thrombosis.

In this 22-year-old man there was involvement of many systems, a patent ductus arteriosus, and one of the most common complications of the Marfan syndrome, dissecting aneurysm of the aorta. The dissection also involved the carotid and subclavian arteries. The medionecrosis was present not only in the aorta but also in the major arteries of the neck, abdomen, legs, and the pulmonary artery.

Case 4

N.D., UH no. 948650, a 27-year-old truck driver, was admitted to the University of Minnesota Hospitals on October 13, 1959, because of shortness of breath and precordial chest pain since February 1959. He was involved in a car accident in the fall of 1958, but developed no cardiovascular symptoms until February 1959. Several pre-employment examinations, as well as physical examinations in the military service when he participated in the Korean War, were all negative. His 64-year-old father has apparently had "heart trouble" since age 30, and his 58-year-old mother has had diabetes mellitus and arteriosclerotic heart disease for 9 years. One brother died of leukemia and three brothers and the patient's two children are apparently in good health and have no skeletal or ocular abnormalities. Physical examination on admission showed a slender, tall man weighing 174 pounds. His height was 78 inches and he had arachnodactyly, high arched palate, and flat feet. The blood pressure was 116/60. There were marked cardiac enlargement, grade-IV systolic and grade-III diastolic aortic murmurs, and a grade-II apical ejection murmur. The liver edge was felt two fingerbreadths below the right costal margin, and the lungs were unremarkable. The venous pressure was 19 cm. (citrate), and the arm-to-tongue circulation time was 20 seconds. Cardiac fluoroscopy revealed marked cardiac enlargement, prominent aorta (fig. 9) and increased pulsations in the arch and ascending aorta. There was left ventricular hypertrophy and strain on electrocardiography. The general condition of the patient gradually deteriorated, the heart failure progressed, and the venous pressure rose to 30 cm. Cardiac fluoroscopy done on October 26, 1959, showed massive enlargement of the heart and diminution in pulsations. A pericardial tap done on October 27, 1959, yielded 400 ml. of bloody fluid containing 3.5 Gm. of hemoglobin in 100 ml. The venous pressure dropped to 15 cm., and the patient gradually improved. A second pericardial tap done on November 12, 1959, yielded 250 ml. of thin, bloody fluid, containing .5 Gm. of hemoglobin in 100 ml. The patient improved further and was able to walk about in his room without great difficulty. He was operated upon at the Minneapolis Veterans Hospital on November 18, 1959, under hypothermia and extracorporeal circulation. There were several hundred milliliters of straw-colored fluid in the pericardial cavity. The aneurysm was saccular and located in the right lateral aspect of the ascending aorta, beginning at the aortic valve and extending to within a centimeter of the innominate artery. It measured

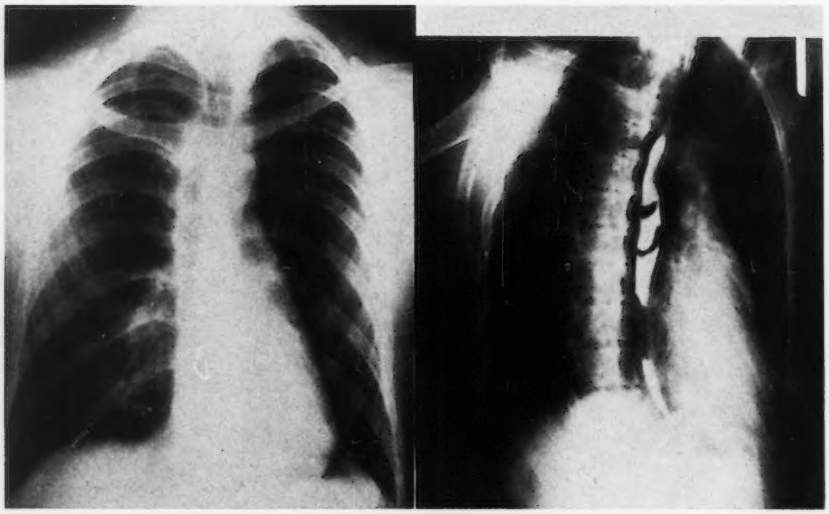

Figure 5

Case 2. Posteroanterior and oblique chest films.

approximately 10 by 8 by 8 cm. The aorta was about 8 cm. in diameter at the level of the aortic ring. There were a harsh systolic thrill over the ascending aorta and moderate left ventricular hypertrophy.

After incising the aneurysm the inner lining of the aorta was seen to be smooth and glistening without evidence of luminal tear. The aortic valve appeared normal except for dilatation of the ring. The aneurysm had ruptured into the pericardial sac. The aortic wall opposite the saccular aneurysm appeared normal; therefore, the saccular portion of the ascending aorta was trimmed back to what appeared to be normal aortic wall and a wedge of sinus of Valsalva was removed from the non-coronary area to narrow the ring. The ascending aorta now appeared to be approximately normal in diameter, and there was no evidence of aortic regurgitation. Microscopically there were many areas of smudgy degeneration of the media, creating small areas of cystic medial necrosis. In one of the sections, there was a dissection of aorta between the media and adventitia, or possibly in the deep layer of the media. This area was recanalized and contained blood. The patient improved markedly after surgery. The heart size decreased, and he was discharged on December 22, 1959.

This 27-year-old man shows the complications of aortic medial necrosis in the Marfan syndrome, namely, dissecting aneurysm with rupture into the pericardial cavity and cardiac tamponade, which were treated surgically.

Discussion

Frequent association of cardiovascular anomalies with skeletal changes of the Marfan syndrome was first pointed out by Salle (1912)[6] and Piper and Irvine-Jones (1926).[7] The reported frequency of such anomalies ranges from 30 to 60 per cent. In the past, it was thought that congenital heart disease, especially interatrial septal defect, was the most common cardiovascular anomaly. Now it is agreed that dilatation of the aorta is more common. Since it involves most frequently the base of the aorta that is intrapericardially located, it may not at first be obvious radiologically. At this stage, aortic regurgitation is frequent, and cardiac fluoroscopy will usually show increased pulsations just above the right atrium. Our cases 1 and 2 demonstrate these points quite well. Both had aortic regurgitation, and routine radiologic studies failed to show the large aneurysmal dilatation of the base of the aorta. This could be demonstrated only by retrograde aortography. Although it is realized that involvement of the aortic sinuses and ring dilatation are the most frequent findings producing aortic regurgitation, ruptured aneurysm of the sinus of Valsalva, and deformities or perforations of the aortic

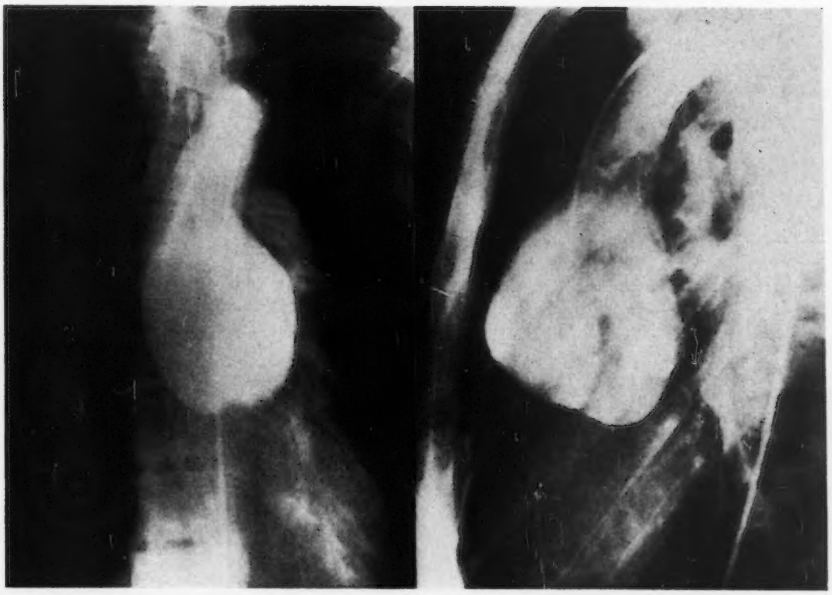

Figure 6

Case 2. Retrograde aortogram, posteroanterior and lateral views, showing large aneurysm involving the root of the aorta and the sinuses of Valsalva. Mild aortic regurgitation was evident on review of further films.

valve, seen in this syndrome, can produce a similar picture. Since some of these anomalies are now surgically correctable, the importance of establishing an accurate diagnosis is quite obvious. Since 1955, Steinberg and his coworkers[8–10] have reported 10 cases of the Marfan syndrome in whom the diagnosis of aneurysms of the sinus of Valsalva was made during life by venous angiocardiography. Except for two patients (nos. 1 and 8) who had normal cardiac silhouettes, all the others had radiologic abnormalities indicating left ventricular enlargement or dilatation of the ascending aorta. The incidence of dilatation of the aortic ring, at autopsy, in cases of Marfan syndrome, has been reported to be about 10 per cent.[11] Histologic studies of the aorta in this syndrome reveal cystic medial necrosis. The aortic involvement usually stops at the level of the innominate artery.[3] The peripheral arteries are generally normal. Austin and Schaefer[12] reported in 1957 the first case showing marked medial necrosis, aneurysmal dilatation, and dissection of innominate, right common carotid, and left common carotid arteries in addition to, but not as a direct result of, dissection of the aorta. Van Buchen[13] reported in 1959 another case with medial necrosis of carotid, femoral, splenic, and renal arteries in addition to involvement of the ascending and descending aorta. In one of McKusick's cases (C. S., UH no. 575946) there was advanced cystic medial necrosis of the splenic artery[4] and, in another case reported by Roark,[14] the lesion involved the splenic, iliac, innominate, both subclavian, both common carotid, both renal, and mesenteric arteries. In our case 3 there was involvement of several arteries in the neck, abdomen, and legs in addition to that of the aorta. In cases 1 and 2, however, biopsies of the femoral artery were normal and there was no evidence of involvement of peripheral arteries.

Surgical treatment of aortic aneurysms or severe aortic regurgitation with heart failure has previously been attempted, but has gener-

Figure 7

Case 3.

ally failed. Aortic regurgitation was treated by the insertion of a Hufnagel valve in Steinberg's case 4, and two other cases with the Marfan syndrome.[15, 16] Since all three ended in failure, it was assumed that the aorta with its medial degeneration was probably unsuited for reparative or palliative surgery.[17] There are several reported cases of the Marfan syndrome in which surgical treatment of the aneurysms of the aorta has been carried out. Bahnson and Nelson[18] successfully plicated the dilated aorta and surrounded the ascending aorta with a splinting sleeve of synthetic fabric in cases with Erdheim's cystic medial necrosis. In two cases with the Marfan syndrome and aortic aneurysm the operation failed.[4, 19] In other cases with this syndrome, however, total replacement of the dilated aortic segments by an autograft, synthetic fabric graft, homograft, and Nylon graft has been successfully performed by Bahnson and others.[20–24] In our case 4 there was marked improvement in the aortic regurgitation after operation. The association of carotid body tumor and this syndrome, as in our case 1, has not previously been reported. However, the relationship, if any, between these two conditions is not clear. There are approximately 300 reported cases of carotid body tumor.

The Marfan syndrome is a hereditary disease due to a mutant gene that produces a defect in the connective tissue. However, the nature of the basic connective tissue defect is not known. No definite abnormalities related to autosomal or sex chromosomes have been found in this syndrome. Experimentally skeletal and vascular changes quite similar to those of the Marfan syndrome have been produced in rats fed diets containing 50 per cent sweet-pea seeds.[25–28] The toxic substance in sweet-pea seeds has been crystallized[29] and identified[30] as β-aminopropionitrile. This substance also can cause skeletal changes and dissecting aneurysm of the aorta.[31] Biochemical studies such as the urinary excretion of hydroxyproline[32] or the changes in the levels of serum mucroproteins or mucopolysaccharides[33] are relatively limited and their significance is not clear. In the absence of specific tests the diagnosis is primarily clinical and relies on family history and the presence of skeletal, ocular, and cardiovascular abnormalities.

There are undoubtedly cases where all the features of the Marfan syndrome are not present; for example, aortic medionecrosis may occur without skeletal and ocular changes. These cases have been described as formes frustes[34–36] of the Marfan syndrome, although their relation to Erdheim's cystic medionecrosis[37, 38] is still not clear. Bahnson suggests that the dilatation of the aorta in the Marfan syndrome extends into the sinuses themselves, whereas in Erdheim's cystic medionecrosis the abnormality is often localized to the ascending aorta.[18]

To confuse the issue still further cystic

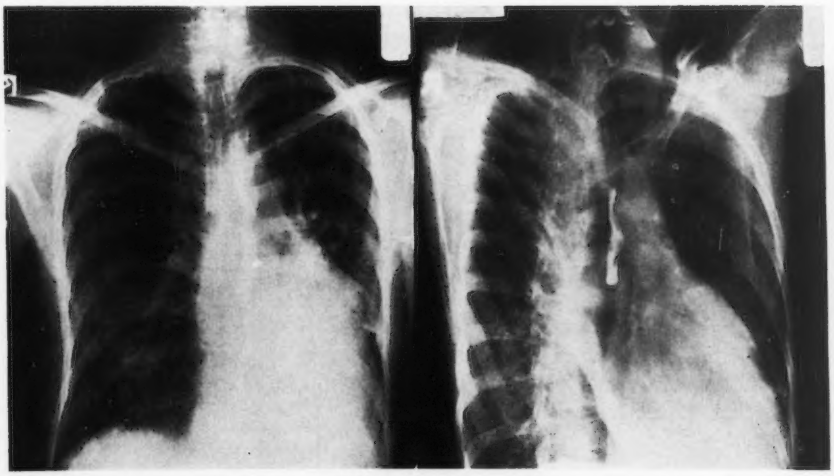

Figure 8

Case 3. Posteroanterior and oblique chest films.

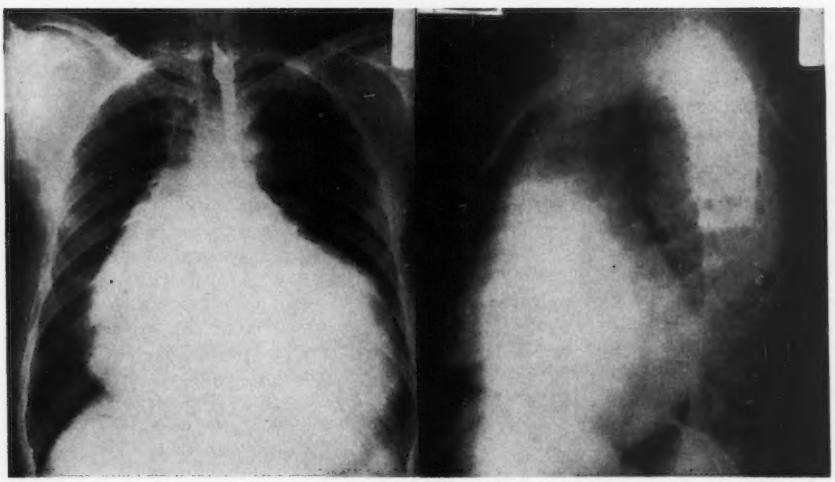

Figure 9

Case 4. Posteroanterior and oblique chest films.

medionecrosis of the aorta has also been described in poststenotic dilatation of aortic stenosis,[23] arterial hypertension associated with coarctation of the aorta, and in some "normal" persons.[40] It is certainly true that Erdheim's cystic medionecrosis or formes frustes of the Marfan syndrome have not been excluded in these cases.

Summary

Four cases of the Marfan syndrome with involvement of the skeletal and cardiovascular systems are reported. In the first two cases with clinical evidence of aortic regurgitation the chest roentgenograms showed relatively normal heart silhouettes while retrograde aortograms revealed large aortic aneurysms

in the intrapericardial portion of the aorta involving the sinuses of Valsalva and the aortic ring. Case 1 had, in addition, a carotid body tumor, which was surgically removed. The remaining two cases had dissecting aneurysms of the aorta. Case 3 died and necropsy showed involvement of many systems and several arteries other than the aorta (carotid, subclavian, renal, femoral, splenic, and pulmonary arteries). Case 4 was surgically treated and showed marked improvement. Problems related to etiology, diagnosis, pathology, and treatment are discussed. It is emphasized that the existence of a large aneurysm of the intrapericardiac portion of the aorta may not be detectable without aortography.

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Thomas Sydenham
1624–1689

Therein lies Sydenham's historical importance, that he turned physicians' attention in a new direction, toward particular illnesses. . . . Whereas for a century investigators had been studying man in general, had been studying illness in general, had been trying with the inadequate methods and instruments of the day to solve the problems of general pathology, Sydenham proclaimed the importance of special pathology. First, he said, let us study particular diseases, let us learn how they make themselves perceptible to us in a particular patient. Let us seek to learn from experience what remedies are best in particular diseases. General conclusions can wait.—HENRY E. SIGERIST, M.D. *The Great Doctors.* New York, W. W. Norton & Co., Inc., 1933, p. 180.

Effects of Acetylcholine on Hemodynamics and Blood Oxygen Saturation in Mitral Stenosis

By C. Alpheus Stanfield, M.D., James K. Finlayson, M.B., Milton N. Luria, M.D., Herbert Constantine, M.D., F. Joseph Flatley, M.D., and Paul N. Yu, M.D.

HARRIS, Wood, Fritts and Shepherd[1-5] have demonstrated that acetylcholine, injected into the pulmonary artery reduces pulmonary arterial pressure in a number of patients with pulmonary hypertension associated with various disease conditions or induced by hypoxia. Wood and co-workers[3] also showed concomitant reduction in pulmonary vascular resistance in patients with mitral stenosis. It was concluded that dilatation of the pulmonary arterial tree did occur during injection of acetylcholine, and that pulmonary hypertension in these patients was at least partly functional in nature.

Recently Söderholm and Werkö,[6] studying patients with rheumatic heart disease, and Chidsey et al.,[7] working on patients with pulmonary emphysema, found that continuous infusion of acetylcholine into the pulmonary circulation frequently produced a significant decrease in arterial blood oxygen saturation associated with a decline in pulmonary arterial pressure and an increase in cardiac index.

Arterial blood oxygen desaturation during acetylcholine infusion might be explained by (a) alveolar hypoventilation resulting from a generalized bronchoconstrictor effect of acetylcholine reaching the bronchial circulation, (b) an alteration in ventilation-perfusion ratios produced by focal bronchoconstriction, (c) the opening of pulmonary arteriovenous shunts that completely bypass the alveoli, or (d) the dilatation of pulmonary arterioles responsible for the perfusion of poorly ventilated alveoli.

The present study was carried out to confirm the previous findings and to investigate the mechanism of acetylcholine-induced arterial desaturation.

Method and Material

Right heart catheterization was carried out in the supine position 2 to 3 hours after a light breakfast. The technics used in this laboratory for (a) determination of cardiac output according to the Fick procedure, (b) measurement of intravascular pressures by transducers, and (c) inscription of indicator-dilution curves, have been previously described in detail in several papers.[8-10]

After a period of slow infusion of 5 per cent dextrose in water, usually in the amount of 50 to 100 ml., and when the patient's ventilation was stable, nearly simultaneous determinations of cardiac output, inscription of indicator-dilution curves and recording of systemic arterial, pulmonary arterial, and pulmonary wedge pressures were made. The data so obtained were used as control values.

Subsequently, solution of acetylcholine chloride,* freshly prepared with 5 per cent dextrose in water to a concentration of 1 mg. per milliliter was continuously infused into the right atrium or main pulmonary artery through a separate opening of a double-lumen catheter or a second catheter. In several cases the solution of acetylcholine chloride was infused into the same catheter through which the pulmonary arterial and pulmonary wedge pressures were recorded.

In each patient the infusion was adjusted to a rate that just failed to produce cough or wheezes. The rate of infusion in most cases was from 2 to 5 mg. per minute. In four cases, a dose of 8 to

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*Merck and Co., Inc., Rahway, New Jersey.

12 mg. per minute was administered. When the maximum effects of acetylcholine infusion were obtained, determination of cardiac output by Fick procedure, recording of intravascular pressures, and inscription of indicator-dilution curves were repeated. Caution was exercised to maintain the rate of infusion or the effects of acetylcholine chloride as constantly as possible.

In 11 patients acetylcholine infusion was continued at the same rate while they were breathing 100 per cent oxygen for 10 minutes. Toward the end of the tenth minute, arterial blood samples were again obtained in all 11, and systemic and pulmonary arterial pressures recorded in six patients.

In seven patients alveolar ventilation, alveolar-arterial oxygen gradient, and arterial blood pH were calculated or determined in the control period as well as during acetylcholine infusion.

Arterial blood carbon dioxide content and oxygen content and capacity were determined by the manometric method of Van Slyke and Neill.[11] During each circulatory state the same sample of arterial blood was used to determine the oxygen content and capacity, and from these values the saturation was calculated. Arterial blood oxygen and carbon dioxide tensions were measured by the method of Riley and associates.[12] Alveolar ventilation and partial pressure of alveolar oxygen were calculated according to the equations described by Pappenheimer et al.[13] Arterial blood pH was measured with a Cambridge research-type pH meter.

Total pulmonary resistance and pulmonary vascular resistance were calculated according to the formulas described by Gorlin and co-workers.[14]

"Central" blood volume[15] is the calculated blood volume in the lungs, the left side of the heart, and the aorta and its large tributaries. The mean transit time indicates the time required for the blood to traverse from the pulmonary artery to the femoral artery.

Data concerning the range of normal variation of different cardiorespiratory parameters in a large series of patients studied in our laboratory have been previously reported.[10, 16, 17] The values were obtained from the same patient in duplicate determinations made at an interval of about 20 minutes. The range was as follows:

Oxygen consumption	(Vo_2)	11%
Respiratory exchange ratio	(R_E)	0.11
Arterial blood oxygen saturation	(S_{a02})	4%
Cardiac index	(CI)	13%
Arteriovenous oxygen difference	($C_{a_{O_2}} - C_{v_{O_2}}$)	0.4 vol. %
Heart rate	(HR)	10 beats/min.
Stroke index	(SI)	7 ml./M.^{2}/beat
Systemic arterial mean pressure	(FA_m)	15 mm. Hg
Pulmonary arterial mean pressure	(PA_m)	5 mm. Hg
Pulmonary wedge mean pressure	("PC"$_m$)	4 mm. Hg
Total pulmonary resistance	(TPR)	25%
Pulmonary vascular resistance	(PVR)	25%
"Central" blood volume	("CBV")	100 ml./M.^{2}
Mean transit time	(T_M)	2 sec.

In a given patient during acetylcholine infusion, any deviation from the above range of variation is considered to be significant.

Eighteen patients with rheumatic heart disease and classical signs of mitral stenosis were studied. The diagnosis was confirmed at operation in 16 patients, while the remaining two patients had no mitral valve surgery because of their mild lesion. There were seven men and 11 women and their ages ranged from 28 to 52 years.

The case number was designated retrospectively according to the degree of arterial blood desaturation observed during acetylcholine infusion. A desaturation of 4 per cent or more (limit of normal variation in our laboratory) occurred in nine patients (cases 1-9), whereas no desaturation or a desaturation of less than 3 per cent was found in the remaining nine patients (cases 10-18). For convenience of description, cases 1-9 are referred to hereinafter as the first subgroup and cases 10-18 as the second subgroup.

Results

As shown in tables 1 and 2, during acetylcholine infusion (a) there was a significant increase in minute ventilation and respiratory exchange ratio for the whole group; (b) a significant decrease was observed in the arterial blood carbon dioxide content, oxygen saturation and oxygen capacity; (c) as a group there was no significant change in either oxygen consumption or arteriovenous oxygen difference. Arteriovenous oxygen difference decreased significantly, however, in six cases of the first subgroup (cases 1 to 9) while it increased significantly in four cases of the second subgroup (cases 10 to 18); (d) for the whole group no significant change was noted in cardiac index, heart rate, pulmonary wedge pressure, total pulmonary resistance, pulmonary vascular resistance, and mean transit

Table 1

*Effect of Acetylcholine Infusion on Minute Ventilation, Oxygen Consumption, Blood Gas Composition, and Arterial Blood Oxygen Saturation**

Case no.	Age, sex	BSA	Periods of study	Dose (mg) min.	$\dot{V}_E$	$\dot{V}_{O_2}$	R_E	$C_{a_{CO_2}}$	$C_{a_{O_2}}$	$C_{a_{O_2}} - C_{\bar{v}_{O_2}}$	CAP_{O_2}	$S_{a_{O_2}}$
1	52	1.56	A		3.49	87	0.86	19.6	17.3	7.4	19.4	89.0
	F		B	3	6.67	84	1.02	18.2	14.9	7.3	18.8	79.0
2	52	1.42	A		4.63	125	0.92	23.5	14.1	5.5	15.5	91.6
	F		B	8	6.00	146	0.95	22.3	13.0	4.8	14.9	87.0
3	29	1.82	A		4.97	148	0.91	22.8	16.1	4.0	17.4	92.7
	M		B	3	5.70	142	0.96	22.4	14.4	3.8	17.1	83.7
4	37	1.72	A		4.93	140	0.85	18.9	17.4	4.6	18.4	94.5
	F		B	12	5.99	149	0.84	18.7	16.0	4.0	19.0	84.0
5	32	1.63	A		3.59	132	0.83	22.6	17.3	5.5	17.8	97.1
	M		B	5	3.80	138	0.80	21.4	16.2	3.4	17.5	92.3
6	38	1.75	A		3.28	123	0.70	21.5	17.1	4.2	17.8	94.5
	F		B	4	4.00	125	0.79	20.8	15.2	3.6	17.6	86.5
7	38	1.60	A		3.12	104	0.87	18.7	18.0	4.1	18.2	99.0
	F		B	9	3.29	103	0.91	18.4	15.7	3.3	17.3	90.1
8	35	1.75	A		3.67	136	0.86	23.0	15.7	4.1	16.5	94.8
	F		B	3	4.10	128	0.97	22.1	14.4	4.4	15.9	90.4
9	42	1.65	A		2.91	100	0.83	23.8	17.4	4.3	18.1	96.0
	F		B	2	4.09	112	0.89	22.4	15.5	3.9	18.0	85.5
10	30	1.71	A		5.16	—	—	22.8	12.7	5.1	14.3	88.6
	F		B	3	4.90	—	—	22.2	12.6	4.9	14.0	90.2
11	30	2.15	A		3.94	122	0.80	21.3	17.5	6.6	18.8	92.9
	M		B	2	3.70	106	0.98	20.1	16.0	6.6	17.6	90.7
12	48	1.76	A		3.62	108	0.90	22.7	18.3	6.2	19.4	94.7
	F		B	12	4.59	119	0.95	21.7	17.3	6.4	19.0	93.1
13	34	1.62	A		2.97	103	0.88	22.2	15.0	5.5	15.5	90.7
	F		B	2	—	—	—	21.6	14.0	5.5	15.5	90.2
14	35	2.02	A		3.19	124	0.89	23.8	18.2	4.4	19.5	93.3
	M		B	3	3.79	158	0.94	23.1	17.6	5.3	19.7	90.5
15	28	1.82	A		3.15	134	0.76	24.1	17.3	3.7	17.8	97.0
	M		B	3	3.70	177	0.92	23.7	16.5	4.2	17.3	95.3
16	31	1.82	A		3.20	109	0.83	21.6	14.6	6.5	14.7	99.9
	F		B	2	3.70	128	0.81	21.4	14.6	8.1	14.2	102.5
17	48	1.86	A		4.85	149	0.77	21.6	17.3	5.3	19.0	91.2
	M		B	2	4.89	140	0.77	21.0	16.5	5.5	17.3	95.4
18	50	1.87	A		2.89	123	0.83	23.6	18.0	4.7	19.0	95.0
	M		B	3	3.10	122	0.79	23.6	17.0	6.0	18.3	93.1
Mean (A-B)					−0.65	−7.1	−0.05	−0.71	1.22	0.04	0.44	4.1
± S.E.					0.20	4.0	0.015	0.11	0.16	0.20	0.12	1.1
p					<0.01	N.S.	<0.01	<0.001	0.001	N.S.	<0.01	<0.01

*BSA = body surface area ($M.^2$)

A = before

B = during acetylcholine infusion

$\dot{V}_E$ = minute ventilation, BTPS (L./$M.^2$/min.)

$\dot{V}_{O_2}$ = oxygen consumption, STPD (ml./$M.^2$/min.)

R_E = respiratory exchange ratio

$C_{a_{CO_2}}$ = arterial blood carbon dioxide content (vol. per cent)

$C_{a_{O_2}}$ = arterial blood oxygen content (vol. per cent)

$C_{\bar{v}_{O_2}}$ = mixed venous blood oxygen content (vol. per cent)

CAP_{O_2} = arterial blood oxygen capacity (vol. per cent)

$S_{a_{O_2}}$ = arterial blood oxygen saturation (per cent)

S.E. = standard error

N.S. = not significant

The symbol of *p* indicates the probability that a difference as large as that observed will occur by chance. A difference with a chance probability of 0.05 or less is considered to be significant.

Table 2

*Effect of Acetylcholine Infusion on Cardiac Index, Heart Rate, Systemic Arterial Pressure, and Pressures, Resistances, and Volume in the Pulmonary Circuit**

Case no.	Periods of study	C.I.	H.R.	S.I.	F.A. S	F.A. D	F.A. M	P.A. S	P.A. D	P.A. M	"PC"m	TPR	PVR	"CBV"	T_M
1	A	1.18	80	15	108	72	80	140	64	88	20	4000	3130	500	23
	B	1.15	56	20	68	44	52	80	36	52	16	2300	1590	470	21
2	A	2.27	105	23	120	72	84	82	38	52	28	1190	520	790	17
	B	3.07	100	31	120	70	84	70	35	48	28	690	280	890	16
3	A	3.74	88	42	92	56	68	60	24	40	30	800	470	930	12
	B	3.70	88	42	84	48	60	46	22	30	22	710	360	930	15
4	A	3.04	80	38	138	88	100	67	30	39	19	600	310	880	19
	B	3.70	80	46	129	87	97	62	32	39	—	490	—	1020	20
5	A	2.40	90	27	125	78	90	48	25	33	20	670	370	980	20
	B	4.05	95	43	125	75	85	44	20	25	24	300	10	1260	22
6	A	2.97	87	34	136	88	100	52	18	32	10	490	280	570	15
	B	2.75	75	46	—	—	—	46	16	28	10	450	290	760	18
7	A	2.52	76	33	108	56	70	40	14	25	20	500	100	860	15
	B	3.14	72	44	100	52	66	34	14	23	18	370	80	1000	18
8	A	3.33	90	37	132	62	77	33	14	17	14	230	40	870	15
	B	2.88	70	41	128	68	82	28	12	16	—	250	—	1230	17
9	A	2.43	88	28	120	64	80	26	8	16	8	310	160	550	13
	B	3.03	86	35	120	64	80	18	6	10	—	160	—	660	14
10	A	4.24†	100	42	115	65	85	100	40	64	28	710	400	760	11
	B	4.27†	95	45	107	67	80	88	32	56	24	610	350	810	11
11	A	1.84	60	31	160	80	100	80	44	56	28	1120	560	880	27
	B	1.60	57	28	152	80	96	68	40	50	20	1160	680	950	25
12	A	1.75	70	25	116	70	88	64	45	49	26	1270	600	520	18
	B	1.87	80	23	112	82	92	59	37	45	26	1100	460	530	18
13	A	1.88	68	28	136	60	80	50	20	30	20	800	270	—	—
	B	—	—	—	100	40	60	44	18	24	20	—	—	—	—
14	A	2.82	100	28	116	60	72	40	24	30	26	390	80	830	19
	B	2.99	100	30	124	60	80	34	20	28	—	400	—	810	19
15	A	3.68	90	41	112	60	76	41	14	26	17	310	110	590	12
	B	4.22	90	47	100	56	68	33	10	19	—	200	—	760	14
16	A	1.67	62	27	136	68	88	32	15	22	20	580	50	800	14
	B	1.57	60	26	136	60	86	34	16	24	—	670	—	870	14
17	A	2.81	72	39	112	68	80	32	16	22	14	340	60	750	16
	B	2.54	68	37	112	60	74	30	14	20	—	340	—	900	17
18	A	2.61	60	44	108	58	72	33	11	18	11	300	120	820	16
	B	2.04	60	34	112	58	76	26	9	13	11	270	40	810	16
Mean (A-B)		−0.19	3.9	−3.8	7.4	3.9	5.2	9.8	4.0	6.0	1.9	196	241	−105	−0.76
± S.E.		0.14	2.0	1.6	3.1	2.2	2.0	3.1	1.5	1.9	1.1	100	150	26	0.39
p		N.S.	N.S.	<0.05	<0.05	N.S.		<0.02	<0.01	<0.02	<0.01	N.S.	N.S.	N.S.	<0.001	N.S.

*C.I. = cardiac index (L./M.²/min.)
H.R. = heart rate (beats/min.)
S.I. = stroke index (ml./M.²/beat)
F.A. = femoral arterial pressure (mm. Hg)
P.A. = pulmonary arterial pressure (mm. Hg)
"PC"$_m$ = pulmonary wedge pressure (mm. Hg)
†Determined by indicator-dilution curve.
TPR = total pulmonary resistance (dynes-sec/cm.⁵)
PVR = pulmonary vascular resistance (dynes-sec/cm.⁵)
"CBV" = blood volume from the pulmonary artery to femoral artery (ml./M.²)
T_M = mean transit time from pulmonary artery to femoral artery (sec.)

time. In five cases of the first subgroup, however, there was an individually significant increase in cardiac index associated with an individually significant decrease in total pulmonary resistance. In only one case of the second subgroup were such changes observed; (e) there were a significant increase in stroke index and a decrease in femoral arterial and pulmonary arterial pressures in the whole group; (f) a highly significant increase in

Table 3

Effect of Acetylcholine Infusion on Alveolar Ventilation, Physiologic Dead-Space, Gas Exchange, and Blood pH

Case no.	Periods	$\dot{V}_A$	V_D/V_T	$P_{A_{O_2}}$	$P_{a_{O_2}}$	$P_{A_{O_2}} - P_{a_{O_2}}$	$P_{a_{CO_2}}$	pH
2	A	2.57	0.45	105	85	20	39	7.39
	B	2.79	0.40	102	62	40	43	7.44
4	A	3.00	0.39	105	79	26	33	7.40
	B	3.94	0.34	114	49	65	32	7.46
5	A	2.69	0.24	108	103	5	40	7.43
	B	2.74	0.26	109	87	22	37	7.44
6	A	3.84	0.33	97	96	1	35	7.37
	B	4.26	0.38	107	78	29	33	7.38
12	A	2.21	0.39	105	99	6	39	7.37
	B	2.48	0.48	105	86	19	39	7.39
14	A	2.24	0.30	114	76	38	38	7.39
	B	2.54	0.33	113	73	40	36	—
15	A	2.48	0.34	114	76	38	37	7.39
	B	3.00	0.27	103	73	30	36	7.39

*$\dot{V}_A$, alveolar ventilation, BTPS (L./M.²/min.); V_D, physiologic dead-space (ml.); V_T, tidal volume (ml.); P_{AO_2}, ideal alveolar air oxygen tension (mm. Hg); P_{aO_2}, arterial blood oxygen tension (mm. Hg); P_{aCO_2}, arterial blood carbon dioxide tension (mm. Hg); pH, pH of whole blood.

the "central" blood volume was found for the whole group. However, individually significant increase was present in seven cases of the first subgroup and in only two cases of the second subgroup.

Table 3 presents some additional data obtained from seven patients. During acetylcholine infusion there was an increase in the mean alveolar ventilation in all patients, but no consistent change in the ratio of the physiologic dead-space to the tidal volume. Although the alveolar oxygen tension showed inconsistent change, the arterial oxygen tension decreased in all seven patients. In the four patients with an arterial oxygen desaturation of more than 4 per cent the alveolar-arterial oxygen gradient increased 17 mm. Hg or more. In the three patients with desaturation of less than 3 per cent or no desaturation, the gradient increased in two patients (13 and 2 mm. Hg, respectively) and decreased in the third. The arterial carbon dioxide tension decreased slightly and pH increased somewhat in most cases.

The combined effects of acetylcholine infusion and inhalation of 100 per cent oxygen in 11 patients are shown in table 4. There was no difference in arterial blood carbon dioxide content or oxygen capacity, regardless of whether room air or 100 per cent oxygen was inhaled. However, inhalation of 100 per cent oxygen increased the arterial blood oxygen content by 1.8 volumes per cent or more in four of five patients of the first subgroup and in three of the six patients of the second subgroup. In all but two patients an arterial oxygen saturation of more than 100 per cent was achieved. With inhalation of 100 per cent oxygen a slight increase in the femoral arterial mean pressure was observed in several patients, but there was no significant change in the pulmonary arterial mean pressure.

Discussion

The results of the present study have shown that acetylcholine infused into the pulmonary circulation produces a significant decrease in the pulmonary resistance, pulmonary arterial pressure, and systemic arterial oxygen saturation in about half of the patients with mitral stenosis studied. These changes were frequently associated with an increase in cardiac index, stroke index, and "central" blood volume. Apparently they were not related to either the magnitude of pulmonary hypertension or the degree of arterial oxygen satura-

Table 4

*Effect of 100 Per Cent Oxygen Inhalation during Acetylcholine Infusion on Blood Gas Composition, Arterial Blood Oxygen Saturation, and Systemic and Pulmonary Arterial Pressures**

Case no.	Periods of study	$C_{a_{CO_2}}$	$C_{a_{O_2}}$	CAP_{O_2}	$S_{a_{O_2}}$	F.A. S	F.A. D	F.A. M	P.A. S	P.A. D	P.A. M
1	B	18.2	14.9	18.8	79.0	68	44	52	80	36	52
	C	18.6	16.2	19.4	83.4	100	68	74	94	42	54
3	B	22.4	14.4	17.1	83.7	84	48	60	46	22	30
	C	21.9	17.7	17.2	103.3	104	72	82	46	22	30
5	B	21.4	16.2	17.5	92.3	125	75	85	44	23	25
	C	20.7	18.2	17.1	107.1	135	85	100	40	14	23
7	B	18.4	15.7	17.3	90.1	100	52	66	34	14	24
	C	16.7	17.5	17.2	101.6	—	—	—	36	14	24
8	B	22.1	14.4	15.9	90.4	—	—	—	—	—	—
	C	22.9	16.6	15.9	104.3	—	—	—	—	—	—
10	B	22.2	12.6	14.0	90.2	107	67	80	88	32	56
	C	24.0	15.2	14.3	106.1	—	—	—	72	40	52
11	B	20.1	16.0	17.6	90.7	—	—	—	—	—	—
	C	21.8	17.5	17.6	99.5	—	—	—	—	—	—
14	B	23.1	17.6	19.7	90.5	124	60	80	34	20	28
	C	22.2	20.6	19.7	104.7	112	60	76	34	20	28
15	B	23.7	16.5	17.3	95.3	—	—	—	—	—	—
	C	22.5	17.6	17.2	101.8	—	—	—	—	—	—
16	B	21.4	14.6	14.2	102.5	—	—	—	—	—	—
	C	22.8	15.2	14.2	106.6	—	—	—	—	—	—
18	B	23.6	17.0	18.3	93.1	—	—	—	—	—	—
	C	22.7	19.4	18.5	104.6	—	—	—	—	—	—

*Symbols used in this table are identical to those defined in tables 1 and 2.
B=Patients breathing room air during infusion of acetylcholine.
C=Patients breathing 100 per cent oxygen during infusion of acetylcholine.

tion prior to the administration of acetylcholine. Some of these findings are in accordance with the observations previously reported by other workers.[1-7]

Since symptoms attributable to the drug, i.e., cough and wheezes, were infrequent while the studies were made, it is unlikely that significant amounts of active acetylcholine reached the bronchial circulation in most patients. The incidence of slowing in the heart rate and reduction in the systemic arterial pressure during acetylcholine infusion was no greater in patients who developed significant desaturation than in those who did not. Furthermore, inasmuch as a decrease in both arterial carbon dioxide content and tension and an increase in calculated mean alveolar ventilation were almost always observed, a general depression of alveolar hypoventilation as a cause of the desaturation may be ruled out.

It is not possible to estimate accurately the pulmonary capillary blood flow (Q_P) in these patients during acetylcholine infusion, since one cannot reasonably assume a normal saturation of the pulmonary venous blood (98 per cent) under this circumstance. However, if the cardiac output determined by the Fick procedure was substituted for the approximate pulmonary capillary blood flow, we found no consistent change in V_A/Q_P during acetylcholine infusion in seven patients who did or did not develop desaturation. This was also true if the pulmonary capillary blood flow was calculated on the assumption that pulmonary venous blood was 98 per cent saturated. Furthermore, the possibility of focal bronchoconstriction was not supported by the inconsistent changes in V_D/V_T during acetylcholine infusion, regardless of whether significant desaturation was present or absent. Further studies of the pulmonary capillary blood flow by the method developed by Lee and DuBois,[18] and of the pulmonary regional

blood flow by the technic described by West and co-workers[19] may be of special interest.

In four of five patients who showed a significant desaturation during acetylcholine infusion while breathing room air, an increase in arterial oxygen content of 1.8 volumes per cent or greater and a saturation of more than 100 per cent was achieved during 100 per cent oxygen breathing while acetylcholine was continued. Thus, the opening of pulmonary arteriovenous shunts that completely bypass the alveoli as a cause for the desaturation seems extremely unlikely.[20]

It is of interest to point out that our unpublished data showed, in most cases, a slight decrease in the pulmonary diffusing capacity for carbon monoxide during acetylcholine infusion.[21] However, this occurred irrespective of the degree of arterial desaturation.

The remaining explanation, that acetylcholine dilates pulmonary arterioles responsible for the perfusion of poorly ventilated regions of the lung, is therefore the most likely explanation for the observed fall in arterial oxygen saturation.

The concept that local alveolar hypoxia resulting from uneven alveolar ventilation may influence the distribution of pulmonary blood flow so as to divert the blood from poorly ventilated areas was first clearly formulated by Von Euler and Liljestrand.[22, 23] More recently, Söderholm and Werkö,[6] and Chidsey et al.[7] have applied this idea in an explanation for the fall in arterial oxygen saturation produced by acetylcholine. According to this formulation, regional alveolar hypoxia results in local pulmonary arteriolar constriction so that systemic arterial oxygen saturation is maintained at relatively high levels at the expense of increased vascular resistance. Acetylcholine, which has been found to counteract the pressor effect of induced hypoxia,[1, 4] may disturb this homeostatic mechanism by dilating the constricted arterioles. This would tend to produce arterial desaturation associated with a decline in pulmonary arterial pressure or an increase in pulmonary blood flow. The bulk of the findings in the present study strongly support this contention.

An almost uniform increase in the "central" blood volume with prolonged mean transit time observed in the group of patients who developed significant desaturation during acetylcholine infusion was further evidence to suggest the occurrence of pulmonary vasodilatation. Any change, however, in the blood volume in the left side of the heart and the aorta and its tributaries could not be ruled out, although it was rather unlikely.

With inhalation of 100 per cent oxygen, despite a possible increase in the pulmonary blood flow in hypoxic regions under the action of acetylcholine, the alveolar oxygen tension was high enough to produce full saturation of the blood. However, 100 per cent oxygen did not further reduce the pulmonary arterial pressure. This observation was somewhat at variance with the findings in patients with congenital heart disease reported by Shepherd and his co-workers.[5] Our results may be explained on the basis that acetylcholine had probably already dilated the pulmonary arterioles to the full extent, and removal of the hypoxic stimulus by inhalation of 100 per cent oxygen failed to exert any further vasodilation.

Our results do not tend to confirm the hypothesis of Bishop et al.,[24] who have recently described the effects of acetylcholine infusion in patients with mitral stenosis breathing 45 to 50 per cent oxygen. They found an increase in A-a gradient and physiologic dead-space in patients with lower pulmonary artery mean pressures (less than 40 mm. Hg) and decrease in these variables in patients with higher pressures. They suggest that in patients with severe pulmonary hypertension unequal ventilation perfusion ratios are produced more by maldistribution of pulmonary blood flow than by uneven alveolar ventilation. In this circumstance dilatation of constricted vessels by acetylcholine, irrespective of the local ventilation, might tend to equalize ventilation perfusion ratios and decrease the A-a gradient and physiologic dead-space.

The changes in $S_{a_{O_2}}$ and A-a gradient observed in our patients during acetylcholine infusion were not related to the control values

of PA_m, $S_{a_{O_2}}$, or $P_{a_{O_2}}$. Significant arterial desaturation developed in three of six patients with pulmonary arterial mean pressures of 40 mm. Hg or more. A-a gradient increased in two patients (cases 2 and 12) with marked pulmonary hypertension and decreased or remained unchanged in two with lower pulmonary artery pressures (cases 14 and 15). These latter two patients did, however, have the highest observed control values of A-a gradient.

Our results throughout the range of pulmonary arterial pressure studied are explicable by the mechanism suggested by Söderholm and Werkö.[6]

Summary

Acetylcholine was infused into the main pulmonary artery in a dose of 2 to 12 mg. per minute to 18 patients with mitral stenosis of rheumatic origin. The drug produced significant arterial oxygen desaturation in nine patients. This was associtaed with (a) a decrease in pulmonary resistance and pulmonary arterial pressure, (b) an increase in cardiac index and stroke index, and (c) an increase in "central" blood volume. The changes in the above parameters were minimal or in opposite direction in those patients who showed no significant desaturation.

The data did not lend support to the explanation that arterial desaturation during acetylcholine infusion was due to (a) decreased alveolar ventilation, (b) focal bronchoconstriction, or (c) opening of pulmonary arteriovenous shunts bypassing the alveoli.

Evidence is presented to show that the most likely mechanism of the decline in arterial oxygen saturation during acetylcholine infusion was an increased pulmonary blood flow in pre-existing poorly ventilated regions of the lungs as a consequence of pulmonary arteriolar dilatation. These changes resulted in a significant lowering of the arterial blood oxygen tension and content, and a considerable widening of the alveolar-arterial oxygen gradient.

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In the growth of human societies small civilisations, however exquisite, have been sacrificed to the formation of vaster and vaster congregations of men; thus only, it would seem, is an equilibrium to be reached of sufficient stability for the highest ends of mankind. Greece, beautiful as was her bloom, penetrating as was her spirit, perhaps because of her very freedom of thought, never became a nation; her city states were too wilful to combine.—THOMAS CLIFFORD ALLBUTT, M.A., M.D. *Science and Medieval Thought.* London, C. J. Clay & Sons, 1901, p. 21.

Association of Specific Behavior Pattern in Women with Blood and Cardiovascular Findings

By RAY H. ROSENMAN, M.D., AND MEYER FRIEDMAN, M.D.

A SPECIFIC overt behavior pattern appeared to us to be a common denominator of clinical coronary heart disease, since for some years we had observed it to be almost invariably present in young and middle-aged men already exhibiting clinical disease. This overt behavior pattern, which we have termed "type A"[1] appeared to us to result from a combination of certain personality traits such as excessive competitive "drive," persistent desire for recognition, advancement and achievement, and persistent inclination for multiple vocational and avocational involvements, on the one hand, and of chronic immersion in "deadlines," on the other hand. The interplay of these endogenous and environmental factors was observed to impart a chronic sense of time urgency, with the propensity or need habitually to accelerate the rate of execution of many if not all physical and mental functions. The key area of harassment in such an individual usually is a seeming paucity of time itself. This "type A" behavior pattern obviously is different from and should not be confused with fear, anxiety or worry states, simple neurosis or similar emotional stresses, as has so often been done in recent medical literature.

Acting on this possible lead we studied[2] a group of accountants before, during, and after isolated exposures to occupational "deadlines" that appeared to induce this behavioral complex acutely in many of them, and found that the latter often exhibited marked increases of serum cholesterol and acceleration of blood coagulation at such times, but independent of changes in diet, weight, or physical activity. We therefore studied[1] groups of men selected for us by lay selectors solely on the basis of their chronic exhibition of the "type A" behavior pattern or a converse "type B" behavior pattern. It was found that men possessing overt behavior pattern "A" also exhibited much higher serum cholesterol levels, more rapid blood clotting, higher incidence of arcus senilis, and a seven-fold higher incidence of coronary heart disease than did either paired subjects exhibiting frank anxiety states, although again the dietary, drinking, smoking, and exercise habits of the three groups were comparable.

In view of these striking differences found in men randomly selected by lay selectors solely on the basis of different but clear-cut overt behavior patterns, it appeared to us of importance to determine whether the possession of behavior pattern "A" would also be associated with higher blood cholesterols and increased incidence of clinical coronary disease in women, such as occurs in this sex when vascular damage and atherogenesis are accelerated by hypertension or diabetes.

Methods of Study

Selection of Two Study Groups

In the selection of subjects exhibiting overt behavior pattern (group A), the aid of six female executives exhibiting the same behavior pattern was enlisted. The characteristics of behavior pattern A were carefully explained to them and they were asked to choose apparently healthy 30- to 59-year-old women, to their knowledge free of clinical cardiac disease, and chosen *solely* on the basis of the exhibition of the various facets of overt behavior pattern A: (1) sustained, aggressive "drive" for achievement, advancement, and recognition, (2) competitiveness and the desire to win, (3) habitual immersion in multiple vocational and avocational involvements subject to the time pressures of "deadlines," (4) extraordinary mental and physical alertness, and (5) the habitual propensity to

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Table 1

Job Classification and Marital Status of 257 Female Subjects

	Overt behavior pattern	
	Pattern A	Pattern B
Total Number*	125	132
% Married	64	84
% Working	97	36
% Married and working	62	20
Work Classification		
Housewife	4	84
Professional	5	0
Executive	84†	1
"White collar"	32	47‡

*Nuns included.
†Included 19 nuns.
‡Includes 20 nuns.

accelerate their pace of execution of most physical and mental functions.

These lay selectors accordingly chose 112 subjects (group A). Each received a letter describing the study and we were gratified that 106 of their selected women accepted the invitation to participate, the remaining six declining on the basis of recent illness, travel, or lack of time. Four of the 106 women (table 1) were not gainfully employed, and there were five attorneys and physicians, 65 business, political, or civic executives, and 32 white collar workers. In order to ensure the inclusion of subjects that did not consume either alcohol or cigarettes, there was an additional 19 nuns of an admittedly forceful order of sisters. Each nun was selected by the Mother Superior who was oriented concerning the characteristics of behavior pattern A.

Upon completing the study of the total 125 group A subjects, the nature of the study was explained to five other lay selectors who were asked to select 30- to 59-year-old women exhibiting the converse behavior pattern B (group B), i.e., women exhibiting placidity, relative absence of drive for advancement and recognition, aggressiveness, desire to compete, ambitiousness, involvement in occupational deadlines, sense of time urgency or the propensity to accelerate speech, mental and physical functions. These lay selectors, chosen by us because of their own exhibition of the behavior pattern B, accordingly selected 139 subjects. Only three of these declined our invitation to participate, but an additional four later were rejected because of medications that might affect the results. Eighty-four of the remaining 132 group B subjects (table 1) were housewives not gainfully employed, and there was one executive secretary and 27 white collar workers. The remaining 20 subjects were obviously placid nuns engaged solely in teaching elementary school, and were selected by the Mother Superior of a separate order of sisters, after orienting her concerning the facets of behavior pattern B.

It is important to emphasize again that the subjects herein studied were selectees, chosen for us by lay selectors *solely* on the basis of their opposing behavior patterns.

The Personal Interview

Each subject carefully completed an advance questionnaire furnishing detailed information about her habitus, catamenia, marital history and parental history of clinical coronary heart disease, her personal medical history, ingestion of drugs, vocational and avocational positions, responsibilities and time pressures, and her habits of smoking, drinking, eating, dietary restrictions, sleep, walking, and other physical exertion. Each of these factors was personally clarified and verified during a subsequent interview with one of us. At the personal interview the degree of development of behavior pattern A or B, respectively, was assessed and recorded by one of us prior to any subsequent procedures. In order to avoid any bias on the part of the authors, all of the subjects were included in the respective groups for which they had been selected by the lay selectors. However, some were adjudged by us at the outset, from the personal interview, to exhibit an incompletely developed behavior pattern A or B, respectively.

Survey of Dietary, Alcohol, and Smoking Habits

Each subject received personal instruction in the diary system which we previously found so successful,[1-3] subsequently recording on a special form the complete consumption of food, alcohol, and cigarettes daily for 7 days, during a week believed characteristic for each subject. Code numbers were used to provide anonymity, thereby avoiding possible reluctance to report all consumption of alcohol, cigarettes, and snacks. The diets were calculated by the chief dietitian of Mount Zion Hospital and Medical Center (Evelyn Piercy, B.S.), who was not informed of the subjects' identity. In about 5 per cent of each group the diaries were either lacking or were not calculated because they failed to exhibit recording of all meals or carefully detailed measurements of portions ingested, nature of sauces or gravies, etc.

Clinical and Laboratory Studies

Following the personal interview and assessment of the completeness of the behavior pattern, each subject was bled once by one of us at 9:00 a.m. to 11:00 a.m. by a two-syringe technic, the first sample being used for duplicate determinations of total serum cholesterol,[4] and of the cholesterol con-

Table 2

Summary of Findings in All 257 Female Subjects

	Overt behavior pattern type			
	Premenopausal subjects		Postmenopausal subjects	
	Pattern A	Pattern B	Pattern A	Pattern B
No. of subjects*	82	110	43	22
Average age (years)	41	38	53	52
Average height (inches)	65.1	64.6	64.3	64.6
Average weight (lbs.)	133	129	139	144
% Married	66	86	49	73
% Parental history of coronary disease	30.4	32.0	23.0	27.0
Catamenia:				
Average age, menarche (years)	13.1	13.2	13.0	12.9
Average duration menses (days)	4.7	4.7	4.6	4.8
% Irregular menses	8.5	9.0	7.0	27.0
Average age at menopause (years)	—	—	46.6	46.5
Smoking:				
% Smokers	55	43	42	9
% Smoking > 20 daily	35	15	19	0
Exercise:				
% Regular exercise	46	65	30	32
Average no. hours/week	2.3	4.1	2.1	4.0
Alcohol:				
% Drinkers	62	54	40	27
Average calories/day	300	135	97	107
Diet (calories):				
Total calories	1772	1848	1746	1694
Protein	299	266	292	271
Carbohydrate	656	761	709	722
Total fats	817	821	745	701
Animal fats	582	535	521	441
Total fat, % of diet	46.2	44.4	42.6	41.4
Clinical findings:				
Average coag. time (min.)	6.70 ± 0.16†	7.35 ± 0.18	6.75 ± 0.18	6.86 ± 0.21
Average serum cholest. (mg./100 ml.)	272 ± 3.7†	214 ± 4.1	300 ± 5.2	249 ± 5.9
% Arcus senilis	23.1	4.5	55.8	22.7
%Diastolic hypertension	24.3	8.2	34.8	4.5
% Clinical coronary heart disease	9.8	2.7	37.2	9.0

*Nuns included.

†Standard error of the mean.

tent or α- and β-lipoproteins separated by filter paper electrophoresis,[5] and the second for determination of blood coagulation time, according to our previously described method.[2] However, the lipoprotein cholesterol content was determined only in 34 group A and 43 group B premenopausal women. These determinations were performed by the same chemists and technicians, respectively, using code numbers for anonymity. In order to avoid the lipid fluctuations of the menstrual cycle,[6] all premenopausal women were bled during the first week following a menstrual period. Prior to venipuncture, the blood pressure was carefully obtained by the author not engaged in interviewing the subjects. The final of several determinations was recorded, and, if elevated, further multiple readings were obtained in order to differentiate sustained from labile elevations. Diastolic hypertension was considered to be present if the diastolic pressure persistently exceeded 95 mm. Hg. The possible presence of arcus senilis was then determined by meticulous gross inspection of both eyes, using frontal and lateral flashlight illumination.

A standard 12-lead electrocardiogram then was obtained. These were interpreted "blind," with use of code numbers by an electrocardiographer not involved in the study (Dr. Herman Uhley, Depart-

ment of Medicine and Electrocardiography, Mount Zion Hospital and Medical Center). No attempt was made to record the frequency of minor, nonspecific abnormalities of contour or rhythm in view of the lack of their specificity with regard to indicating the presence of coronary disease; if abnormal, they were considered by the electrocardiographer to be diagnostic of ischemic heart disease only if the tracing exhibited a diagnostic pattern of healed myocardial infarction or characteristically abnormal T waves not ascribable to hypertrophy, conduction defects, or other abnormal cardiac or known extracardiac causes.

Finally, each subject was closely questioned about possible heart disease of any cause and specifically for a possible history of myocardial infarction or angina pectoris. The former diagnosis was not accepted unless verified by the electrocardiogram, and the latter was not entertained unless the subject described classical acute episodes of squeezing substernal pain, with or without radiation, precipitated by exercise or acute emotional upset, and relieved readily by rest or nitroglycerin or both and unless the diagnosis was accepted by both authors from independent questioning.

Because of the long-suspected influence of the menopause upon coronary morbidity in women, the two groups of subjects have been subdivided on the basis of this factor for purposes of presentation of the data.

Results

Accuracy of the Assessments of the Behavior Patterns by the Lay Selectors

As shown in table 1, 106 lay subjects were selected for us as exhibiting behavior pattern A. Although none of them were assessed by us during their personal interview as exhibiting the converse pattern (i.e., behavior pattern B), we believed that 56 of these 106 subjects exhibited an incompletely developed form of behavior pattern A.[1] Similarly, of the 112 lay subjects selected for us as exhibiting behavior pattern B, we ourselves considered 25 of these as exhibiting an incompletely developed form of pattern B. In view of the fact, however, that the incompletely developed forms of each behavior pattern resembled their respective completely developed forms far more than they did each other, we have presented below the data of each group as it was chosen for us by our selectors.

The assessment by the Mother Superiors of the 19 nuns exhibiting behavior pattern A and of the 20 nuns exhibiting pattern B appeared to us to be accurate with one exception. Whether such agreement was due to a better comprehension by the Mother Superiors of the two behavior patterns or to necessarily more intimate knowledge of their subordinates, we do not know.

Marital and Employment Status

As can be seen in table 1, 97 per cent of group A women and 36 per cent of group B women worked outside of their homes. The larger percentage of working women in group A was due, we believe, to the fact that some of the facets making up this behavior pattern (e.g., deadlines, competition, etc.) are most often found in the commercial or industrial phases of community living. It can also be noted in table 1 that 64 per cent of group A and 84 per cent of group B women were married, and that more than three times as many women in group A (62 per cent) were both married and working than in group B (20 per cent).

The Premenopausal Subjects

Age, Height, Weight, Catamenia, and Parental History of Coronary Disease

One hundred ninety-two women (including the nuns) were still menstruating (table 2). Eighty-two of these had been assessed for us by the lay selectors as exhibiting behavior pattern A (group A) and 110 as exhibiting pattern B (group B).

The average age of the group A women was 41 years and that of group B women, 38 years. Their average heights and weights (table 2) were approximately the same, as was their incidence of parental coronary heart disease. Similarly, no difference was found in their menstrual histories.

Smoking, Exercise, Sleep and Drinking Habits

There were more women in group A (55 per cent) than in group B (43 per cent) that smoked and more group A women (35 per cent) smoked over one package of cigarettes daily than in group B (15 per cent).

More women in group B (65 per cent) than in group A (46 per cent) regularly exercised and devoted more time weekly to this. More group A women performed regular morning

bedside calisthenics and more group B women did gardening activities. It is doubtful that the recorded differences are significant, however, since in no instance could any subject in this study be said ever to indulge in even moderately heavy physical activity. There were no significant differences in sleep patterns.

Sixty-two per cent of group A and 54 per cent of group B women ingested alcoholic beverages, but the average daily consumption of alcoholic calories was considerably greater among the former (table 2), particularly in the younger age groups. This was found due to the propensity of many of the female executives of group A to have one or more cocktails at their frequent "business" lunches.

Dietary Habits

As can be noted in table 2, there were no significant group differences in average daily intake of total calories, proteins, carbohydrates, total or animal fats, or the percentages of the total caloric intakes composed of fats. Although the diets were carefully recorded and calculated, it is doubtful whether the minimal noted differences are significant.

Blood Coagulation, Serum Cholesterol, and Lipoprotein Cholesterol

The blood coagulation time averaged 6.70 minutes in group A women compared to 7.35 minutes in group B. It is possible that these differences are even more significant in view of the known effect of anxiety on accelerating blood coagulation time, since far more women of group B than group A exhibited excitement and anxiety about the studies. This was probably due to the fact that many more group A women were accustomed to having annual medical examinations at their own behest as well as in connection with their employment.

Highly significant differences were noted in the serum cholesterol levels (table 2). Thus, the serum cholesterol averaged 272 mg./100 ml. in group A women, compared to 214 mg./100 ml. in group B women. These differences were even more striking in comparing those subjects adjudged by us at the outset to exhibit the completely developed behavior patterns, averaging 281 mg./100 ml. (S.E. Mean: ±5.3) in 45 subjects adjudged by us to exhibit all facets of behavior pattern A, compared to 211 mg./100 ml. (S.E. Mean: ±3.3) in the 91 subjects we believed exhibited completely developed pattern B. There were no differences found in the lipoprotein distribution of the total serum cholesterol, the α/β lipoprotein cholesterol content averaging 27.5/72.5 per cent in group A subjects and 28.1/71.9 per cent in group B subjects.

Clinical Findings

Arcus senilis was observed in 23.1 per cent of group A women compared to 4.5 per cent of group B women (table 2). Similarly, a much higher incidence of diastolic hypertension was found in group A (24.3 per cent) than in group B (8.2 per cent) women. Clinical coronary heart disease was detected in eight group A women (9.8 per cent) compared to three group B women (2.7 per cent). The diagnosis was made in six of the eight group A women and in all of the group B women from the electrocardiographic findings, a clear-cut history of angina pectoris being obtained in the other two women of group A, but in none of the group B women.

The Postmenopausal Subjects

Age, Height, Weight, Catamenia, and Parental History of Coronary Disease

Sixty-five women were postmenopausal (table 2), of which 43 had been assessed for us by the lay selectors as exhibiting behavior pattern A and 22, pattern B.

The average age of the group A women was 53 years and that of group B women, 52 years. There were no significant differences of average height, weight, catamenia, or average age at menopause (table 2). The latter was influenced by its early occurrence after hysterectomy in some subjects of each group.

Smoking, Exercise, Sleep, and Drinking Habits

In table 2, it can be seen that more of the women in group A (42 per cent) than in group B (9 per cent) smoked and only certain group A (19 per cent) women smoked over 20 cigarettes daily. There were no differences in habits of exercise or sleep. More women in group A (40 per cent) consumed alcoholic

Table 3

Summary of Findings in Two Groups of Nuns

	Overt behavior pattern type			
	Premenopausal subjects		Postmenopausal subjects	
	Pattern A	Pattern B	Pattern A	Pattern B
No. of subjects	9	14	11	5
Average age (years)	42	40	55	46
Average height (inches)	67.0	65.9	64.0	65.4
Average weight (lbs.)	151	140	147	143
% Parental history of clinical coronary disease	11	28	36	40
Catamenia:				
Average age, menarche (years)	13.1	12.7	13.1	13.8
Average duration of menses (days)	4.1	4.4	4.0	4.2
% Irregular menses	0	0	0	20
Average age at menopause (years)	—	—	47	38
Diet (calories):				
Total calories	1703	1593	1683	1504
Protein	270	240	271	219
Carbohydrate	736	715	757	696
Total fats	697	638	655	589
Animal fats	503	458	461	405
Total fats, % of diet	41.5	40.2	39.3	38.7
Clinical findings:				
% Arcus senilis	11.0	0	36.4	20.0
% Diastolic hypertension	22.0	21.4	36.4	0
Average coagulation time (min.)	6.9	6.4	6.4	6.2
Average serum cholest. (mg./100 ml.)	266 ± 8.2*	204 ± 8.6	305 ± 14.1	269 ± 8.9
% Clinical coronary heart disease	33.0	7.1	54.5	0

†Standard error of the mean.

beverages than in group B (27 per cent), but the average daily intake of alcoholic calories by the group A women was slightly less (table 2).

Diet

The average intake of calories and their distribution were very similar in the two groups (table 2), as was the percentage of the total calories derived from total fats and animal fats.

Serum Cholesterol and Blood Coagulation Time

As in the premenopausal subjects, there were highly significant differences of average serum cholesterol levels, which averaged 300 mg./100 ml. in group A women, compared to 249 mg./100 ml. in group B women. If only subjects were considered that were adjudged by us at the outset to exhibit the completely developed behavior patterns A and B, respectively, the average serum cholesterol levels were 318 mg./100 ml. (S.E. Mean: ±8.8) in 24 group A women and 247 mg./100 ml. (S.E. Mean: ±10.0) in 16 group B women. On the other hand, there were no significant differences of average blood coagulation time (table 2).

Clinical Findings

Arcus senilis was observed in 55.8 per cent of group A women compared to 22.7 per cent of group B women (table 2). Similarly, a much higher incidence of diastolic hypertension was observed in group A (34.8 per cent) than in group B (4.5 per cent). A systolic blood pressure persistently exceeding 150 mm. Hg also was found in 37 per cent of group A compared to only 14 per cent of group B women. Clinical coronary heart disease was found in 16 group A women (37.2 per cent) compared to two group B women (9 per cent). The diagnosis was made from the electrocardiographic findings in 10 of the 16 group A and all of the group B women, a history of myocardial infarction being obtained in two

group A women and of angina pectoris in the remaining four group A women.

The Findings in Two Groups of Nuns

The findings in the two groups of nuns (table 3) were of particular interest to us despite their small numbers, since none of the subjects ever consumed alcoholic beverages or smoked and none indulged in physical activity other than walking. Each nun in group A (convent A) was selected by her Mother Superior on the basis of her exhibition of pattern A personality traits, and because she was simultaneously both teaching and an executive at a parochial college, an administrative executive of her Order, engaged in one or more community activities and admittedly subject to chronic harassment from paucity of time per se as a result of her multiple vocational and avocational involvements. The nuns of group B (convent B) had been selected by their Mother Superior because of the total absence of all of the above factors, being engaged vocationally only in teaching in an elementary grade school, in addition to her religious functions.

The Premenopausal Nuns

The average age was 42 years in nine group A nuns and 40 years in 14 group B nuns. The nuns of group A were slightly taller and heavier, but had a small incidence of parental coronary heart disease (table 3). The dietary intakes of calories and various food categories were slightly greater in group A nuns, but were not significant when calculated in terms of body surface area. A similar percentage of the diet was derived from fats in both groups. Arcus senilis was observed only in group A nuns (11 per cent). A tendency to rapid blood coagulation was observed in almost all the nuns of both groups. As in the lay subjects, there were striking differences of serum cholesterol levels, which averaged 266 mg./100 ml. in group A and 204 mg./100 ml. in group B. Clinical coronary heart disease was found in three nuns (33 per cent) of group A compared to one nun (7.1 per cent) of group B, the diagnosis being made from electrocardiographic findings in all nuns.

The Postmenopausal Nuns

The average age of 11 group A postmenopausal nuns was 55 years, compared to 46 years in five group B nuns. The latter's earlier age was ascribable to the earlier surgically induced menopause of three of the nuns of this group. As can be noted in table 3, there were no differences of height, weight, or parental incidence of clinical coronary disease. The average age of the women at the time of their menopause was 47 years in group A and 38 years in group B. Only minor differences were noted in the diets of the two groups (table 3).

Arcus senilis was observed in 36.4 per cent of group A, compared to 20 per cent of group B nuns, and diastolic hypertension was found only in group A nuns (36.4 per cent). There were no differences of average blood coagulation time, but significant differences again were noted in serum cholesterol levels, which averaged 305 mg./100 ml. in group A and 269 mg./100 ml. in group B. Clinical coronary heart disease was found in six group A nuns (54.5 per cent), the diagnosis being made from the electrocardiographic findings in all but one nun from whom a history of angina pectoris was obtained. Clinical coronary disease could not be detected in any of the five group B nuns.

Analysis of Subjects with Clinical Coronary Heart Disease

Inspection of tables 2 and 3 indicates that clinical disease was found about four times as frequently in both the premenopausal and postmenopausal women of group A than in group B. There were eight additional instances where markedly slurred, notched, and broadened ventricular complexes with abnormal T waves were found in the electrocardiograms, but not considered diagnostic of ischemic heart disease. It is of interest, however, that arcus senilis was present in three of them and that seven of these eight tracings were obtained from women in group A.

When the 24 cases of clinical coronary heart disease in group A and the five in group B were more closely studied (table 4), it was found that in addition to the presence of pat-

Table 4

Comparative Findings in Subjects with and without Clinical Coronary Heart Disease

	Overt behavior pattern type				All subjects	
	Pattern A		Pattern B			
	With heart dis.	Without heart dis.	With heart dis.	Without heart dis.	With heart dis.	Without heart dis.
No. of subjects	24	101	5	127	29	228
Average age (years)	48.2	44.2	45.0	40.0	47.7	42.0
Average height (inches)	64.3	65.1	63.4	64.7	64.2	64.9
Average weight (lbs.)	135	137	130	132	134	134
% Obese	16	7	0	5	14	6
% Parental history	33	29	0	30	28	29
Catamenia:						
Average age, menarche (years)	13.3	13.1	13.6	13.0	13.4	13.0
% Irregular menses	8	10	20	12	10	11
% Postmenopausal	67	27	40	16	62	21
Average age at menopause (years)	46.0	47.0	49.0	26.0	48.0	46.5
Diet (calories):						
Total calories	1671	1780	1710	1831	1678	1807
Total fats	720	800	700	802	716	801
Animal fats	466	580	460	518	464	546
% Regular exercise	28	37	65	65		
Sleep, average hrs./night	7.5	7.5	8.0	7.8	7.6	7.7
Smoking:						
% Smokers	42	52	20	39	38	45
% Smoking > 20 daily	13	23	20	9	14	15
Alcohol:						
% Drinkers	21	70	60	53	24	60
Average calories/day	157	258	192	129	170	195
Clinical findings:						
% Diastolic hypertension	41	24	0	8	34	15
% Arcus senilis	58	29	20	7	52	17
Average coag. time (min.)	6.6	6.7	6.8	7.2	6.7	6.9
Average serum cholest. (mg./100 ml.)	296	277	217	220	283 ± 10.9*	243 ± 3.3
Ratio: *No. of pattern A* / *No. of pattern B*	—	—	—	—	4.8	0.8

†Standard error of the mean.

tern A in the great majority of them (83 per cent) there was also (table 4) an increased incidence of menopause (300 per cent), diastolic hypertension (227 per cent), obesity (233 per cent), and arcus senilis (300 per cent) as compared to the remaining subjects of both groups A and B who appeared free of the disease. It is probable, too, that the average serum cholesterol (283 mg./100 ml.) of the subjects with clinical disease was significantly higher than that (243 mg./100 ml.) of the healthy persons of both groups.

On the other hand, such factors as average height, weight, the catamenia, the dietary intake of total calories and of total and animal fats, the ingestion of alcohol, the smoking of cigarettes, exercise, the presence or absence of parental history of coronary artery disease, and the time for blood coagulation appeared to be the same in both the total group of subjects with and those without clinical coronary heart disease. Certainly the finding of as much or higher incidence of ischemic heart disease in the respective groups of nuns, as compared to that found in the lay subjects, indicates clearly the failure of either cigarettes or alco-

hol to intensify the incidence of the disease under investigation in our subjects.

Many women with clinical disease were employed outside the home (83 per cent). The factor of working per se did not appear of etiologic significance, however. Thus, although clinical disease was observed mainly in working group A women, it was found only in one of 48 working women in group B and was absent in a total of 145 working women of both groups. The nature of the work appeared to have greater significance, however. Thus, although only 35 per cent of all subjects were in professional and executive occupations, 62 per cent of women with clinical disease were in these occupations. In contrast, although 65 per cent of the subjects were white collar workers or did not work outside the home, only 38 per cent of those with clinical disease were found among the latter subjects.

The high incidence of clinical disease in women in the executive occupations in this study of course is influenced by the choice of subjects by the lay selectors and a similar high incidence might not be found in a survey of a much larger random female population. It is certainly a simplification to state that, as found by us earlier in males exhibiting behavior pattern A,[1] the key area of harassment of all group A female subjects and particularly in those in the executive occupations was their great sense of time urgency and chronic lack of time for their usually multiple occupational duties, and many avocational involvements in clubs, societies, charitable organizations, civic and community activities, etc., types of involvements and recurrent deadlines almost entirely absent in the group B women. The latter housewives, of course, were often faced with different types of time pressures and emotional harassment as in usual household activities, "carpools" for children, etc. However, the same pressures also were present in many of the 60 per cent of the executive women that also were married and the latter women were readily able to differentiate the nature of these deadlines and time pressures consequent to their occupational and avocational obligations outside the house compared to the emotional and other stresses found in the home.

Discussion

The preceding observations obtained from a study of 257 women (including 39 nuns) selected solely by lay selectors who also assessed their behavior pattern suggest certain conclusions that appear to us to be valid.

First, that when the criteria characterizing what we have termed behavior patterns A and B were employed carefully to distinguish and separate premenopausal and postmenopausal female subjects, such separation resulted in two groups of subjects who did not show any significant differences in their average age, height, weight, incidence of parental ischemic heart disease, dietary consumption of total calories or of total or animal fat, involvement in physical activity, or in their catamenia.

However, both premenopausal and postmenopausal women exhibiting behavior pattern A also exhibited certain differences from their counterparts exhibiting pattern B. Thus, the pattern A women smoked more cigarettes, drank more alcohol, had a far higher incidence of arcus senilis, much higher serum cholesterol levels, and, among the premenopausal subjects, a significantly faster clotting time. These differences were similar to those previously found in men exhibiting behavior patterns A and B.[1] The difference in serum cholesterol levels in the female subjects is even more striking if one considers that the serum cholesterol exceeded 275 mg./100 ml. in 77 per cent of group A compared to 19 per cent of group B women, and exceeded 300 mg./100 ml. in 29 per cent of group A, but in less than 2 per cent of group B subjects. Conversely, serum cholesterols less than 225 mg./100 ml. were found in 59 per cent of group B, but only in 8 per cent of group A women.

The detection of four times as much clinical coronary heart disease in both the premenopausal and postmenopausal females exhibiting behavior pattern A as compared to the analogous females with pattern B, was similar to our earlier findings[1] in two similarly chosen groups of men who, although ingesting ap-

proximately isocaloric and "isolipid" diets, and indulging in approximately the same amount of exercise, nevertheless exhibited a similar marked discrepancy in their proclivity to clinical coronary disease.

The group of men with pattern A that exhibited this marked increase in coronary morbidity also smoked more and drank more alcohol, but after analysis of the internal data available[1] we did not find that either of these habits could be held responsible for their increased incidence of heart disease. The present study and comparison of a group of women (nuns) indulging in neither habit confirmed our earlier conclusion that the increased smoking and drinking indulged in by individuals with pattern A were associative rather than causative factors in the increased coronary disease morbidity of this particular group.

The increased incidence of coronary heart disease in the postmenopausal women with either pattern A or B is, of course, a finding to be expected. We are not prepared at this time to conclude whether this increased incidence is due to altered thrombogenic propensity or other metabolic change consequent to diminished hormone secretion or the relatively increased age per se. Certainly the equal or almost equal sex incidence of coronary heart disease of many non-Caucasian groups[3] argues strongly against any specific female sex hormone protection against this disease and rather suggests that the higher incidence of coronary morbidity in males in this and other Western societies is due to factors enhancing the disease in this sex. Our earlier study in men[1] indicated that the group of subjects found to have clinical coronary disease was of the same average age (48 years) as that of the present group of female subjects having clinical disease. If such men had an associated drastic sex phenomenon, it escaped both their and our attention.

A finding of great interest to us was the three- to seven-fold higher incidence of diastolic hypertension found in both premenopausal and postmenopausal women exhibiting pattern A as compared to their counterparts with pattern B. The mechanism responsible for this striking difference in subjects chosen solely because of their psychologic traits by lay selectors is not known by us. The association of diastolic hypertension with coronary heart disease in 34 per cent of our subjects was not a surprising phenomenon, however, in view of their already well-known relationship. The unexpected finding, however, of far more hypertension in all subjects with pattern A, whether or not clinical coronary disease was present, makes it difficult to determine whether this particular disorder played a major causal role in the coronary heart disease when coexisting in our subjects or whether both are only associative consequents of the behavior pattern itself.

It is questionable whether the greater incidence of obesity found in the cardiac subjects is significant. Certainly in our earlier study with males[1] no such increased incidence was found. Clinical disease was detected in four (22 per cent) of 18 obese women (weight exceeding 10 per cent greater than the ideal weight in the Metropolitan Life Insurance Company Standard Table) compared to 25 (10.5 per cent) of the nonobese females. On the other hand, the association of obesity and clinical disease was found only in group A, since clinical disease was not found in any of the obese subjects of group B.

Again as in this earlier study,[1] the markedly greater incidence of arcus senilis both in the group A women and in subjects with clinical disease was impressive. Its possible relationship, however, to the also present coronary heart disease or to some mechanism common to both remains unknown to us.

The mechanism whereby behavior pattern A increases the proclivity to clinical coronary heart disease remains to be fully clarified.[7] We have not previously[1] or in the present studies found it ascribable to differences in diet, cigarette smoking, alcohol consumption, physical activity, or hereditary incidence of clinical coronary disease. The finding of a hastened blood coagulation time both in our earlier studies[1, 2] and in the present study in premenopausal subjects with pattern A, of

course suggests that this particular factor may serve as a causal mechanism. We realize the insecurity of any conclusion based upon single determinations taken upon the small number of cardiac subjects, using a relatively crude external measure of thrombogenic proclivity. It is one reason that we ourselves continue to harbor only the suspicion rather than the conviction that it may well be that the subject with behavior pattern A consistently indulges in precisely those aggressive, competitive, and accelerated activities that, if indulged in by animals, do hasten the clotting time quite markedly.[8] Other known attributes of subjects possessing behavior pattern A that may be of possible causal importance in their increased incidence of clinical coronary disease are their higher blood pressures, higher serum cholesterol levels,[1] and augmented daytime secretion of norepinephrine.[9]

Throughout this study, we have emphasized a behavior pattern and its association with increased incidence of clinical coronary disease. Such emphasis, however, should not be misconstrued as evidence that the relatively high dietary ingestion of cholesterol and fat by Western man plays a minor role in the pathogenesis of coronary artery disease. It is our present belief that this Western dietary with its propensity to elevate the serum cholesterol of man from his natal level of approximately 100 mg./100 ml. furnishes the basic area in which the entrance of this particular behavior pattern wreaks its additional damage. On the other hand, the present and our previous[1, 2] observations again emphasize the hazard of ascribing to diet alone the mechanism responsible for serum cholesterol levels exceeding 225 mg./100 ml. in either sex, as well as indicating that, in a population where an overabundance of calories and fats in the diet is ubiquitous and probably so for many decades,[10] diet alone cannot account for either the selective advent of clinical disease in certain subjects nor for the latter's considerable increase in recent decades. It would be of extraordinary interest to us to learn what effect, if any, this behavior pattern might have upon subjects whose ingestion of cholesterol and fat is almost nil. Such a study seems never to be accomplished, since unfortunately, whether one follows the Negro, the Oriental, or the Yemenite as he enters Western society, concomitant with his exposure to and increasing assumption of facets of this particular behavior pattern, his intake of cholesterol and fat inexorably proceeds to increase. Conversely, these same groups in their native habitat, not only ingest low-fat diets but differ in innumerable variables, not to mention the absence of most facets of pattern A.

We would like to emphasize once more that behavior pattern A is neither a flagrant neurosis nor characterized by anxiety or other simple emotional stresses; it is a seemingly almost normal mode of living variously indulged in by perhaps millions of Americans. Unlike a neurosis, it has received more admiration than condemnation by most citizens. Its very ubiquitousness, its frequent capture even of the physician and researcher himself, its ability at times to afford both economic and social rewards are all characteristics that have acted to obscure its apparent adverse association with clinical coronary heart disease. Then too, its inability to be measured in classical quantitative terms and its lack of an epidemiologic base have favored its neglect—a neglect that we believe has become increasingly perilous in most current clinical and epidemiologic studies.

Summary

The possible effect of a specific overt behavior pattern upon serum cholesterol levels, blood coagulation, and incidence of arcus senilis and clinical coronary heart disease was studied in two groups of women randomly chosen for study by lay selectors after careful orientation. Women of group A were selected on the sole basis of their habitual exhibition of a behavior pattern (type A) characterized by excessive competitive "drive," ambitiousness, and immersion in "deadlines." Women of group B were selected by lay selectors on the sole basis of their exhibition of entirely opposite behavioral traits (type B). Each group of subjects included a series of nuns respectively exhibiting the type A and B be-

havior patterns. The women exhibiting pattern A also exhibited markedly higher serum cholesterol levels, often more rapid blood coagulation, three to five times as much arcus senilis, three to seven times more diastolic hypertension, and a four-fold higher incidence of clinical coronary disease. A history of myocardial infarction or angina pectoris only was found in group A. These striking differences were independent of differences in parental incidence of coronary disease, caloric or fat intake, obesity, physical activity, smoking, or "femininity." The strikingly higher incidence of clinical disease in pattern A women also was not found ascribable per se to differences in heredity, obesity, hypertension, caloric or fat intake, smoking, physical activity, blood coagulation, or serum cholesterol levels.

The results closely resemble those previously found in men with similar behavior patterns, and strongly suggest that the type A behavior pattern is itself in some way largely responsible for the observed findings.

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Effect of Digitalis in Patients Receiving Reserpine

By BERNARD LOWN, M.D., LEE EHRLICH, M.D., BERNARD LIPSCHULTZ, M.D., AND JOHN BLAKE, M.D.

RECENTLY, we encountered an unusual response to digitalis. A patient with rheumatic valvular disease, congestive heart failure, and atrial fibrillation exhibited simultaneously evidence regarded by some as due to underdigitalization and by others as the result of overdigitalization. During mild exertion, the ventricular rate accelerated from 70 to 140 beats per minute with development of a pulse deficit suggesting inadequate digitalization. At the same time, however, this patient developed ventricular bigeminy with multiform complexes suggesting digitalis intoxication (fig. 1). In order to clarify this anomalous situation, a digitalis tolerance test was performed with acetyl strophanthidin.[1] The first small increment of acetyl strophanthidin provoked ventricular bigeminal rhythm (fig. 2), a response consistent with digitalis overdosage. Mild exercise immediately following the test, however, again accelerated the rate to 140, a response compatible with underdigitalization. Thus the paradox of apparent coexisting evidence suggesting both overdigitalization as well as underdigitalization remained unsolved.

This patient was receiving many medications. With the exception of reserpine, which was being administered in a daily oral dose of 1.0 mg., none of the other drugs appeared likely to alter the response to digitalis. A search of the literature did not reveal significant information concerning the effects of reserpine upon the digitalized state. The present study was therefore undertaken to determine (1) whether reserpine alters the toxic action of digitalis upon atrium, atrioventricular conduction system, and ventricle; (2) whether the carotid sinuses are unduly sensitized by the combined use of these two drugs; and (3) whether reserpine can control the ventricular rate in the partially digitalized patient with atrial fibrillation.

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Material and Methods

The sensitivity of the myocardium to digitalis was tested with acetyl strophanthidin both immediately before and during the administration of reserpine. Acetyl strophanthidin is a synthetic aglycone of strophanthin. When it is given intravenously, a cardiac effect occurs within 3 minutes. Peak action develops in 12 minutes, and dissipation is complete within 2 hours.

Fifteen patients in congestive heart failure were studied. All were receiving maintenance doses of one of the long-acting digitalis preparations. Six were in normal sinus rhythm and nine had atrial fibrillation. Two of the patients with normal sinus rhythm had coronary artery disease, one rheumatic valvular disease, two cor pulmonale, and one idiopathic myocarditis. Of the patients with atrial fibrillation eight had rheumatic valvular and one had coronary artery disease.

The same experimental design was employed in each of the 15 patients. Two digitalizations were carried out in identical manner: 0.15 mg. of acetyl strophanthidin in 2.5 ml. of diluent was injected intravenously every 5 minutes until development of the earliest evidence of intoxication or the administration of a total dose of 1.2 mg. Nausea, vomiting, and a change in rhythm or in conduction constituted the toxic end-point. This schedule represents a slight modification in the use of acetyl strophanthidin from that proposed initially.[1] The reduction in the size of the incremental dose has enhanced the safety of such ultra-rapid digitalizations.

Immediately following the first digitalization 1 mg. of reserpine was given intramuscularly. This was continued daily for 3 days. On the third day, a second digitalization with acetyl strophanthidin was repeated. Prior to and immediately following each of the two digitalizations, the sensitivity of the heart to right carotid sinus massage was tested. This maneuver was employed to assess the cardiac

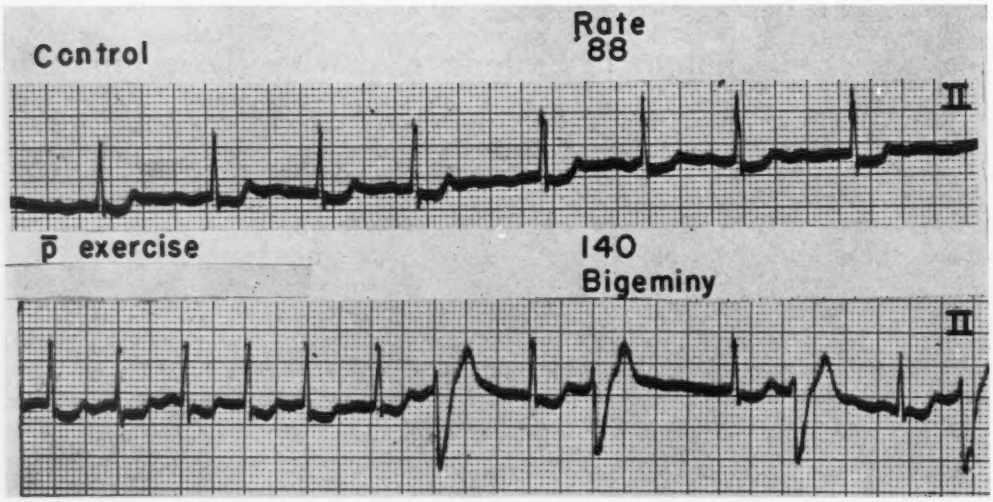

Figure 1

Exercise accelerated ventricular rate to 140, suggesting inadequate digitalization. Simultaneous development of ventricular bigeminal rhythm indicated digitalis intoxication.

response to vagus nerve stimulation when reserpine and digitalis were combined. Throughout this study there was no change in the maintenance dose of the long-acting digitalis preparations that these patients were receiving.

In addition, three of the patients with atrial fibrillation were subjected to mild exercise consisting of 10 sit-ups, accomplished before and after each of the two digitalizations.

Results

Patients with Atrial Fibrillation

Reserpine increased the toxic action of digitalis. This was clearly demonstrated in patients with atrial fibrillation. In the digitalization following reserpine, the tolerated dose of acetyl strophanthidin was reduced, the incidence or arrhythmias was increased, and the heart was more markedly slowed (table 1A).

In five of the nine patients with atrial fibrillation, after reserpine, the tolerated dose of acetyl strophanthidin was reduced. In these five patients, the mean tolerated dose of acetyl strophanthidin was 1.1 mg. in the first and 0.5 mg. in the second digitalization. The electrocardiogram in one of these five patients is illustrated (fig. 3). In the initial digitalization only one patient developed an arrhythmia before receiving the full dose of 1.2 mg. In the second digitalization, however, eight of the nine subjects exhibited toxicity consisting of complete heart block in one, nodal rhythm in three, and ventricular ectopic beats in five. In four of the five, the ventricular extrasystoles were either bigeminal or multiform. Another example of increased cardiac reactivity to acetyl strophanthidin is shown in figure 4. In this patient during the control digitalization, 1.2 mg. of acetyl strophanthidin merely slowed the ventricular rate; following reserpine, however, an identical dose of acetyl strophanthidin induced nodal rhythm with 3:2 antegrade block below a complete atrioventricular block with periodic ventricular escape beats. This same patient illustrates the remarkable slowing in heart rate that results from the combined action of reserpine and digitalis. In the entire group of nine patients with atrial fibrillation, the mean ventricular rate was reduced from 75 to 61 in the first and from 55 to 42 beats per minute in the second digitalization.

Patients with Normal Sinus Rhythm

In patients with normal sinus rhythm reserpine did not appear to alter the response

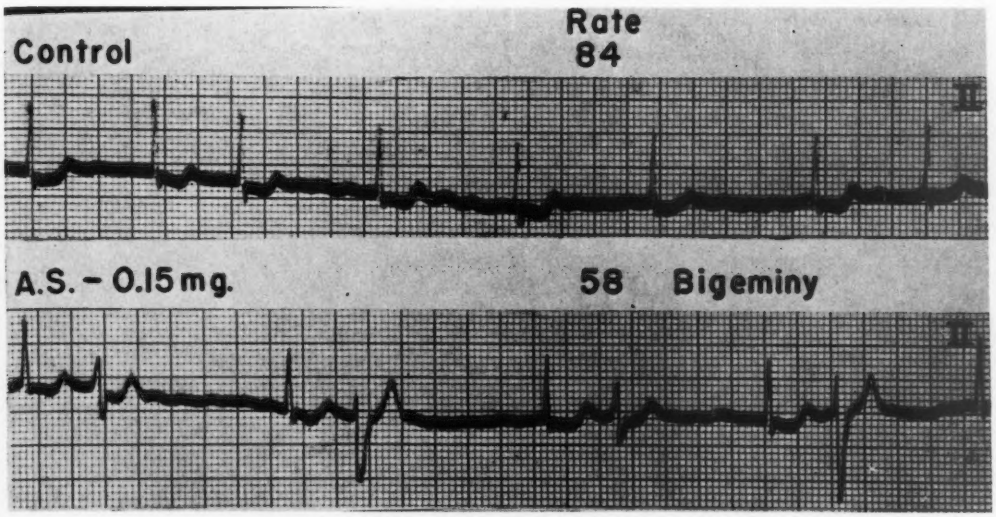

Figure 2

Same patient as in figure 1. A single increment of 0.15 mg. of acetyl strophanthidin induced multiform ventricular bigeminal rhythm.

to digitalization (table 1B). Five of the six patients with normal sinus rhythm were digitalized twice. In none of the five was there a change in the dose of acetyl strophanthidin or in the incidence of toxic reactions following reserpine.

In order to determine whether reserpine increased the sensitivity of the heart to vagal stimulation in digitalized patients, with either sinus rhythm or atrial fibrillation, the carotid sinus on the right side was massaged on four different occasions, i.e., before and after each of the two digitalizations. Both acetyl strophanthidin and reserpine increased the cardiac response to this vagal maneuver. The most marked effect was noted when the two drugs were used together (table 2). Abnormal reactions exclusive of heart rate slowing were observed in three of the 15 patients before the first digitalization. Two of these three patients were unable to tolerate the full dose of 1.2 mg. of acetyl strophanthidin. When the carotid sinus was stimulated immediately after the first digitalization, abnormal reactions occurred in seven of the 15 patients. Carotid sinus stimulation after reserpine administration but before the second digitalization induced an abnormal response in nine of the 15 subjects. In one of these patients the vagal maneuver provoked ventricular bigeminal rhythm. The carotid sinus was tested in only 11 of the patients who were digitalized after reserpine, the four remaining patients showed advanced toxic reactions from acetyl strophanthidin and were therefore not considered to be suitable candidates for this maneuver. Of the 11 patients tested, nine reacted abnormally, two exhibiting bigeminal rhythm. Since the four patients in whom carotid sinus massage was not repeated had reacted adversely to vagal stimulation before the second digitalization, it is likely that following the digitalization with acetyl strophanthidin a similar but more marked response would have occurred. Thus 13 out of the 15 patients might have shown enhanced responsiveness to the carotid maneuver after both drugs.

In the digitalized patient, reserpine promotes bradycardia. To determine whether the slowing is maintained after exertion, three patients with atrial fibrillation were made to exercise before and after the two digitalizations. Though reserpine slowed the mean ventricular rate from 90 to 70 beats per minute

Table 1A

Results of Digitalization with Acetyl Strophanthidin before and after Reserpine in Nine Patients with Atrial Fibrillation

Patient	Before reserpine				After reserpine			
	Dose AS (mg.)	Heart rate Initial	Heart rate Final	Toxic* reaction	Dose AS (mg.)	Heart rate Initial	Heart rate Final	Toxic* reaction
1. R.M.A.	1.2	60	40	None	1.2	40	32	None
2. M.K.	1.2	70	68	None	1.2	55	32	Nodal rhythm
3. R.N.	1.2	79	58	None	1.2	56	32	Nodal rhythm with 2:1 block
4. J.W.	1.2	60	42	None	1.2	52	42	Occasional VPB
5. B.R.	1.2	92	70	None	0.6	68	40	Multiform VPB nodal rhythm
6. A.S.	1.2	80	68	None	0.75	64	50	Ventricular bigeminy
7. G.C.	0.9	80	64	Occasional VPB	0.45	60	40	Ventricular bigeminy (multiform)
8. F.M.	1.2	80	35	None	0.6	55	40	Ventricular bigeminy
9. E.M.N.	1.2	70	50	None	0.3	45	38	Complete heart block

*Exclusive of nausea.
AS = Acetyl strophanthidin.
VPB = Ventricular premature beats.

Table 1B

Results of Digitalization with Acetyl Strophanthidin before and after Reserpine in Six Patients with Sinus Rhythm

Patient	Before reserpine				After reserpine			
	Dose AS (mg.)	Heart rate Initial	Heart rate Final	Toxic* reaction	Dose AS (mg.)	Heart rate Initial	Heart rate Final	Toxic* reaction
1. A.N.	1.2	100	88	None	1.2	84	72	Sinus pauses with nodal escape
2. W.C.	1.2	100	94	None	1.2	105	104	None
3. B.J.	0.6	87	75	Ventricular bigeminy	0.75	72	38	VPB
4. M.S.L.	1.2	98	77	None	1.2	90	85	None
5. M.H.	1.2	105	100	None	1.2	108	88	None
6. J.M.S.	0.9	82	80	Ventricular bigeminy	Heart block after reserpine, not retested with A.S.			

*Exclusive of nausea.

at rest, it did not prevent cardiac acceleration (table 3). Exercise raised the heart rate to the same level whether or not reserpine was given. Only digitalization controlled the ventricular rate during and after exercise.

Discussion

This investigation was undertaken to explain the occurrence of ventricular bigeminy in a patient having rapid heart rate and atrial fibrillation. The results of the present study afford an explanation for this phenomenon. When a digitalized patient who is receiving reserpine exhibits bradycardia and ventricular premature beats, the maintenance dose of digitalis is reduced. Since the rauwolfia alkaloids do not increase cardiac contractility, they cannot be substituted for the cardiac glycosides. Though the heart rate may continue to be slow at rest, with inadequate digitalis maintenance therapy cardiac decompensation might nevertheless recur. In the patient with atrial fibrillation, the earliest evidence of heart failure would consist of excessive

Table 2

Effect of Carotid Sinus Stimulation in 15 Patients Receiving Acetyl Strophanthidin and Reserpine

Reserpine	Acetyl strophanthidin	Number tested	Abnormal response
0	0	15	3
	+	15	7
+	0	15	9 (1B)†
	+	11*	9 (2B)

*In four of the 15 patients severe toxic reaction precluded the carotid sinus maneuver.

†B = Ventricular bigeminy provoked by carotid sinus stimulation.

Table 3

Effect of Reserpine and Acetyl Strophanthidin upon Ventricular Rates in Three Patients with Atrial Fibrillation

Reserpine	Acetyl strophanthidin	Mean ventricular rate	
		Rest	Exercise
0	0	90	123
	+	66	93
+	0	71	119
	+	64	94

ventricular acceleration during exercise. The findings also indicate that reserpine sensitizes the myocardium to the induction of ectopic beats by digitalis. Since myocardial aerobic metabolism is seriously compromised during tachycardia, it seems likely that ventricular extrasystoles would be more readily produced by such drug interaction when the heart rate is rapid. In the patient with atrial fibrillation the end result may be bigeminal rhythm and a rapid ventricular rate.

Reserpine increases central parasympathetic outflow thereby augmenting vagal tone. In the present study this was demonstrated by response to carotid sinus stimulation before and after administration of reserpine. Of 15 patients tested only three had abnormal reactions to carotid sinus massage initially as contrasted to nine such reactions after pretreatment with reserpine.

It is well established that digitalization also sensitizes the heart to vagal discharge. Carotid sinus stimulation may be employed to detect overdigitalization before it becomes otherwise evident.[2] The emergence in the digitalized patient of heart block, nodal rhythm, or ectopic beats during this vagal maneuver suggests incipient intoxication. It is of interest that two of the patients who developed untoward reactions during the initial carotid sinus test were unable to tolerate the full dose of acetyl strophanthidin. These two were also the only patients to develop ventricular bigeminal rhythm during the control digitalization. In the patient receiving reserpine, therefore, an adverse response to carotid sinus stimulation does not constitute evidence of overdigitalization.

The vagal action of reserpine has been employed to control various atrial arrhythmias.[3, 4] In an occasional patient reserpine has proved effective in preventing supraventricular arrhythmias.[5] Reserpine materially reduces the immediate mortality from ventricular fibrillation in dogs subjected to acute coronary artery ligation.[6] Less well known is the finding that rauwolfia alkaloids may precipitate ventricular premature beats. Wilson and Wimberley[7] described four patients in whom Raudixin in a dose of 100 to 200 mg. per day produced numerous ventricular extrasystoles and bigeminy. Only one of the patients was receiving digitalis. Schreader and Etzl[8] noted an increased incidence of ventricular ectopic beats in patients receiving both rauwolfia alkaloids and digitalis. Thus of 15 patients receiving both drugs, seven showed ventricular extrasystoles as contrasted with three of 15 patients who were receiving only rauwolfia alkaloids.

The mechanism by which reserpine predisposes to ventricular ectopic beats is unknown. Scherf and Schott[9] have demonstrated that stimulating the vagus nerve in dogs receiving a cardiac irritant such as aconitine, induces ventricular extrasystoles and other ventricular arrhythmias. The enhanced ventricular automaticity shown in the present study may be due to such a vagal effect. An alternative mechanism may be suggested. Reserpine lib-

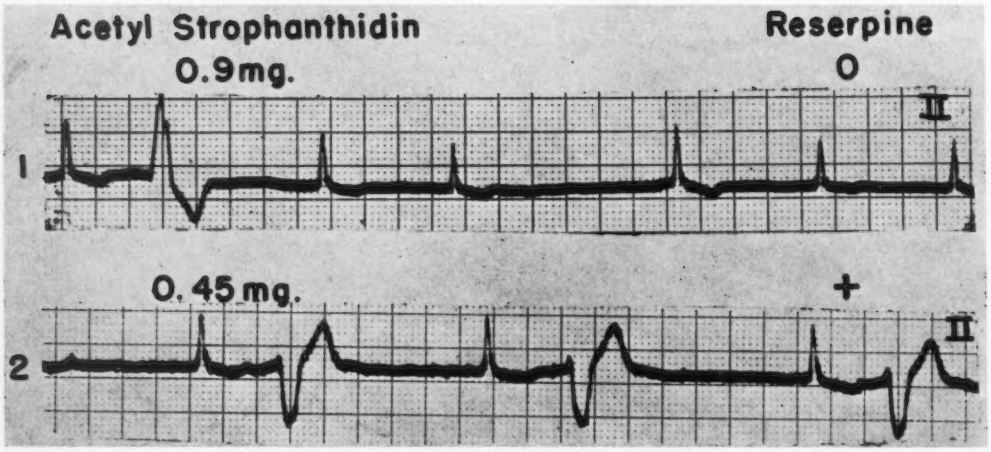

Figure 3

A dose of 0.9 mg. of acetyl strophanthidin produced but a rare ventricular premature beat. After the administration of reserpine for 3 days, only half the control dose of acetyl strophanthidin was tolerated and resulted in the development of ventricular bigeminal rhythm.

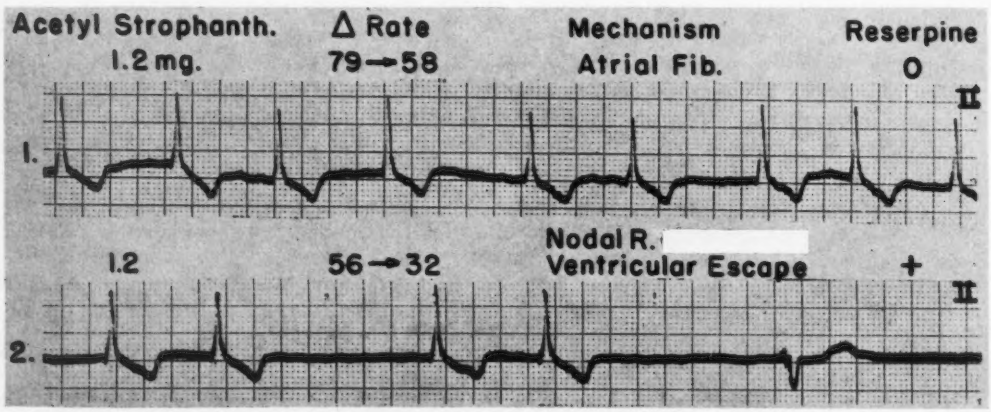

Figure 4

Acetyl strophanthidin slowed ventricular rate from 79 to 58 without altering underlying mechanism of atrial fibrillation. After reserpine same dose of acetyl strophanthidin induced nodal rhythm with 3:2 antegrade block and occasional ventricular escape beats.

erates catechole amines from peripheral stores.[10-12] Small intravenous doses deplete cardiac norepinephrine.[11] The absence of neurohumoral transmitter inhibits the peripheral adrenergic system. The marked potentiation of epinephrine action by reserpine may be due to such a loss of norepinephrine from nerve endings thereby resulting in a functional sympathetic "denervation."[13] Adrenal medullary innervation is cholinergic. If, in the reserpine-treated subject, digitalis enhances the action of acetylcholine at this site, it may then predispose to increase catecholamine release during exercise or excitement and favor the development of ventricular arrhythmias.

It is of interest that reserpine potentiation

of digitalis action was observed only in patients with atrial fibrillation. Gold and Otto[14] first called attention to the fact that digitalis-provoked bigeminal rhythm was more likely to occur in patients with atrial fibrillation as compared to those having sinus rhythm. Thus among 240 patients with atrial fibrillation 17 per cent exhibited digitalis bigeminy, whereas among 615 cardiac patients with normal sinus rhythm only 2.8 per cent had such an arrhythmia. It is not clear why the presence of atrial fibrillation should favor the occurrence of digitalis-induced ventricular ectopic beats. There is much evidence indicating that atrial fibrillation reduces the cardiac output and compromises cardiac efficiency. Presumably deterioration in cardiac function may be the necessary background for exhibition of the reserpine digitalis interaction.

The clinical implication of the findings here reported is that the commonly used indices of overdigitalization may prove deceptive in patients with serious heart disease who are receiving reserpine. Thus marked bradycardia, ventricular ectopic beats, and even bigeminal rhythm as well as abnormal responses to carotid sinus stimulation may not denote overdigitalization. These manifestations may indeed occur in patients who are inadequately digitalized.

Summary and Conclusions

Reserpine enhanced the toxic action of the digitalis-like drug, acetyl strophanthidin, upon the atria, atrioventricular conduction system, and ventricles. This potentiation was demonstrated only in patients with atrial fibrillation. While eight of nine patients in atrial fibrillation who were receiving reserpine developed advanced toxic rhythms during acute digitalization, only one patient responded in this fashion when reserpine was not given. Patients receiving reserpine were unable to tolerate full doses of acetyl strophanthidin.

Reserpine increased cardiac sensitivity to carotid sinus stimulation. This was true irrespective of heart rhythm, and was most marked when the patient received digitalis as well.

Reserpine did not prevent significant acceleration in the ventricular rate following exercise.

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The Surgical Significance of Aberrant Renal Arteries in Relation to Systemic Hypertension

By JOHN R. DERRICK, M.D., AND KENNETH R. T. TYSON, M.D.

IN A PREVIOUS PAPER we reported a strong statistical correlation between the incidence of aberrant renal arteries and the incidence of systemic hypertension.[1] We have since seen three clinical cases of systemic hypertension, the origin of which could be traced directly to segmental renal ischemia secondary to insufficiency of an aberrant renal artery.

Case Reports

Case 1

A 7-year-old boy was first seen by his local pediatrician in October 1956, with complaints of polydipsia, polyuria, and enuresis. Blood pressure recordings at this time were equal in all extremities and were elevated to as high as 260/150 mm. Hg. Intravenous pyelography and a phentolamine (Regitine) test were reported as negative. In November 1956, the patient underwent exploratory laparotomy. The findings were negative.

He was referred to the University of Texas Medical Branch in December 1956, at which time a translumbar aortographic study was attempted without success. Antihypertensive therapy was instituted with equivocal results, the blood pressure remaining at levels around 160/110 mm. Hg.

In April 1959, selective arteriography of the renal arteries was performed.[2] Premature arborization of the right renal artery was apparent, with an area of stenosis and poststenotic dilatation in a small branch that entered the superior segment of the kidney (figs. 1 and 2).

On April 25, 1959, the right renal artery was exposed at laparotomy. The artery branched into several small vessels almost immediately after its point of origin from the aorta, and a small branch to the superior segment was stenotic at its origin from the larger vessel. A significant pressure gradient was found over the stenotic area (fig. 3). The area of stenosis was resected, and the vessel was reanastomosed primarily.

The patient's postoperative course was characterized by a progressive drop in blood pressure to normotensive levels. The polyuria, polydipsia, and enuresis disappeared. Two years after the date of operation the blood pressure was 115/80 to 100/76. The patient is completely asymptomatic.

Case 2

A 58-year-old man was seen by his local physician because of persistent throbbing headaches of approximately 2 months' duration. There was no history of hypertension. He was referred to the University of Texas Medical Branch for evaluation because of the headaches, a history of nervousness, 9 months of insomnia, and a blood pressure of 280/150 mm. Hg. At the time of physical examination, his blood pressure was 270/128 mm. Hg. A grade-I systolic murmur was audible over the base of the heart. At this time the heart was considered to be enlarged. Intravenous pyelograms were negative. On selective arteriograms of the renal arteries, bilateral aberrant renal arteries to the lower pole of each kidney were demonstrable.

In March 1960, laparotomy was performed. Aberrant renal arteries were found to be supplying both lower poles. There was a significant pressure gradient across the orifice of the right aberrant renal artery. The orifice was severely compromised by diffuse subintimal atheromatous thickening. Both aberrant renal arteries were 1.5 mm. in diameter, and were, therefore, considered to be too small for grafting. Silk ligatures were used to tie off both of the aberrant arteries.

Postoperatively, the blood pressure declined gradually, from 160/90 mm. Hg, without antihypertensive therapy. In the 9 months the patient has been followed, his blood pressure has varied from 180/90 to 210/100 without antihypertensive therapy.

Case 3

A 12-year-old Negro girl was first seen in February 1958, at the University of Texas Medical Branch, because of frontal headaches and left flank discomfort. On physical examination, blood pressure was 140/100 mm. Hg in all extremities, and there was grade-2 hypertensive retinopathy. Findings were normal on intravenous pyelography.

The patient received antihypertensive therapy with little benefit. Blood pressure ranged from 130/100 to 160/120 mm. Hg. On translumbar aortography in October 1958, opacification of both

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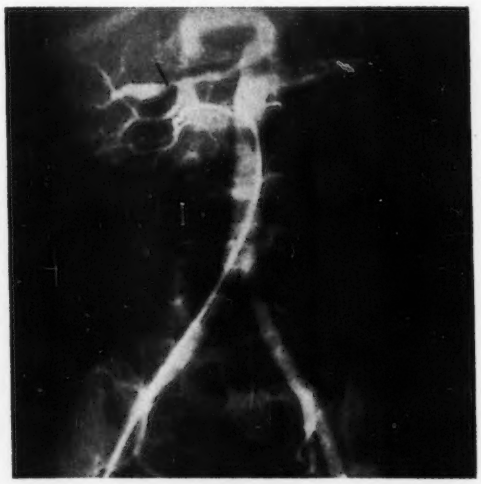

Figure 1

Selective arteriogram in case 1. The catheter tip is at the level of the second right lumbar artery. Note the stenotic area at the take-off of the superior branch of the right renal artery and the poststenotic dilatation distal to the constriction.

kidneys was normal, but the right renal artery was not visible. The blood pressure dropped to a level of 120/80 with bed rest, low-salt diet, and treatment with antihypertensive drugs.

Moderate caliectasis of the right kidney was discernible on intravenous pyelograms, and findings on urinalysis were consistent with pyelonephritis. After antibiotic therapy urine cultures were sterile. With ambulation the blood pressure again rose to hypertensive levels.

On selective renal arteriograms on April 4, 1960, the right renal artery was well visualized, and the lower pole of the right kidney did not fill (figs. 4 and 5). On subsequent injection, a small artery to the lower pole of the right kidney was visible.

On May 6, 1960, laparotomy was performed. A hypoplastic aberrant renal artery to the lower pole of the right kidney was found. There was no pressure gradient across the right main renal artery, but the small aberrant vessel accommodated only a 22-gage needle. Although there was a large pressure gradient between this vessel and the aorta, recordings were severely damped. The vessel was believed to be too small to permit revascularization, and segmental renal resection was not considered feasible at the time; hence, the aberrant vessel was ligated in the hope that conversion of the area of ischemia to one of infarction would alleviate the hypertension.

Blood pressure recordings 10 to 12 days postoperatively ranged from 130/90 to 118/70. During the 7-month follow-up period, the patient's blood pressure has remained 130/90. The continued mildly elevated blood pressure may indicate a zone of relative ischemia between the infarcted area and the adjacent kidney parenchyma.

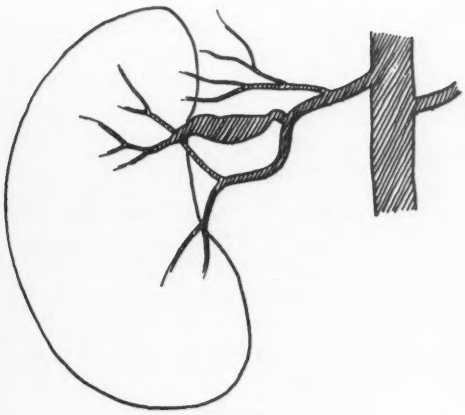

Figure 2

Diagram of right renal arterial morphology as seen by selective arteriography in case 1.

Discussion

The concept of systemic hypertension secondary to renal ischemia is well accepted.[3-5] Any process that causes ischemia of the renal parenchyma may produce systemic hypertension by the formation of the pressor substance, angiotensin. The kidney is divided into five distinct arterial segments, between which there is no appreciable anastomosis.[6] Since aberrant renal arteries are truly segmental renal arteries with different origins,[7] it is logical to conclude that vascular insufficiency of an aberrant renal artery may produce segmental renal ischemia and subsequent systemic hypertension. Indeed, cases of segmental renal ischemia causing systemic hypertension have been reported.[8, 9] A return of the blood pressure to normotensive levels has occurred after segmental resection of the affected kidney.[9]

Partial occlusion of an aberrant renal artery that results in decreased blood supply to one or more renal segments may be congenital in origin, manifesting itself as an isolated stenosis of that artery. Case 1 is an example

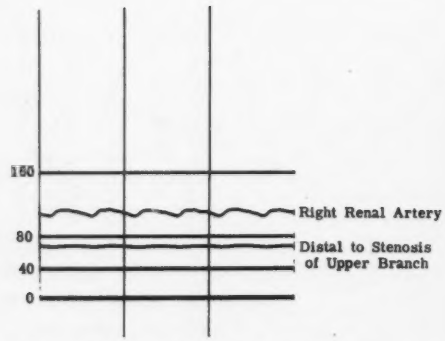

Figure 3

Case 1, pressure gradient across stenosis of upper branch of right renal artery.

of such a stenosis. In addition, the entire aberrant vessel may be hypoplastic, as Howard et al.[10] and Isaac et al.[11] have reported (case 3). Segmental renal ischemia on the basis of partial occlusion of an aberrant renal artery may result from atheromatous encroachment upon that artery's lumen, and thus may occur as an acquired form. Gyori[8] has reported 10 such cases. Our second case is an example of diffuse atheromatous deposition that caused constriction at the aortic orifice of an aberrant renal artery.

The effect of the most advanced lesion of arterial insufficiency, that is, infarction, is much less well delineated in relation to segmental renal involvement. Systemic hypertension rarely occurs as a result of infarction of an entire kidney,[12] and, when it does occur, it is usually transient. The relationship between segmental renal infarcts and the production of systemic hypertension, is, however, much less clear. Gross[13] stated that, in surgery for ureteropelvic obstruction secondary to an aberrant renal artery, it is possible to divide the offending vessel with impunity. He had seen only one case of hypertension thought to have occurred from this mechanism. Hoxie and Coggin[14] were unable to correlate hypertension with segmental renal infarcts in their study of 205 cases; yet Arnold et al.[15] have

Figure 4

Case 3, selective arteriogram of right main renal artery. The inferior renal segment does not fill. A subsequent injection revealed a very small artery coursing to the inferior pole of the right kidney.

reported two cases of transient hypertension after ligation of aberrant renal arteries, and have suggested that such transient hypertension may be common. Numerous authors[15–20] have reported cases of sustained severe systemic hypertension after segmental renal infarction. It seems, therefore, that complete occlusion of a segmental renal artery, specifically an aberrant renal artery, may result in no hypertension, transient hypertension, or sustained systemic hypertension, and, at present, there is no way to discern preoperatively whether a segmental renal infarct is the offending entity in the production of hypertension.

Until better diagnostic methods are devised, we consider that any hypertensive patient in whom no other cause for hypertension can be found, and who has, potentially, 15 to 20 good years left, should have the benefit of renal arteriography in an attempt to delineate the etiology of his hypertension. The technic of renal arteriography should be of such quality

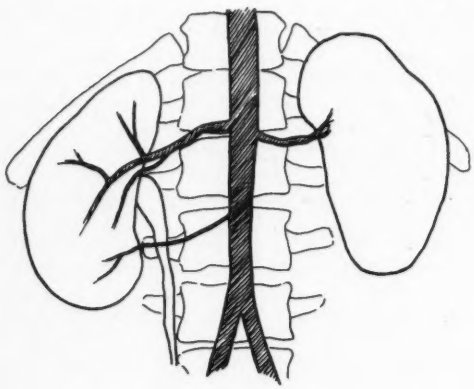

Figure 5

Case 3, diagram of right renal arterial morphology demonstrated by selective arteriography.

that all five renal arterial segments may be visualized.[21] We have used primarily the technic of selective visceral arteriography[2]—retrograde arterial catheterization—with good results. There is need, however, for defining more clearly the radiologic criteria for arterial narrowing that is sufficient to cause renal ischemia.

In the choice of surgical procedures for relief of hypertension secondary to segmental renal ischemia, revascularization of the ischemic area should be considered first. Morris et al.[22] has emphasized the fact that the "ischemic" portion of the kidney may actually be the better-functioning portion, after revascularization, since it has been protected from the nephrosclerotic effect of the hypertension it produced. Revascularization of an ischemic renal segment may be accomplished in a number of ways. We have used primary resection of the stenotic area of an aberrant renal artery, as in case 1, and transplantation of the origin of an aberrant vessel, as in case 2. If the aberrant vessel in question is too small to consider revascularization, as in case 3, the artery may be tied off and the ischemic area converted to a frank infarct, or a segmental resection of that ischemic portion of the kidney may be made. A small incidence of hypertension after segmental renal infarcts is unavoidable; hence, ligation of the vessel may not relieve the hypertension. Total nephrectomy should, however, be avoided whenever it is possible.

Summary

Three cases of hypertension associated with vascular insufficiency of aberrant renal arteries are presented. Two patients were subjected to revascularization procedures. The types of pathologic processes associated with aberrant renal arteries in production of segmental renal ischemia are discussed. Considerations of diagnosis and therapy of such lesions are reviewed.

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One drawback of the present popular confidence in research is that the donors of research funds have overlooked or underestimated the importance of the medical education that will provide an adequate supply of good researchers in the future. The donors have also ignored the importance of giving first-rate research men today the salaries and tenure they deserve. As between donor and recipient, the relationship, especially in short-term grants, suggests a grim variant of the declaration that it is more blessed to give than to receive—it is certainly more comfortable. For the plain fact of the matter is that most of our medical schools often find that the full cost of research is not covered by the grants which are supposed to pay for it. The schools cannot afford any longer to accept the full moral responsibility, but only part of the full cost, of many research projects.—ALAN GREGG, M.D., *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 72.

Effect of Thiazide Diuretics on Plasma Volume, Body Electrolytes, and Excretion of Aldosterone in Hypertension

By Ray W. Gifford, Jr., M.D., Vernon R. Mattox, Ph.D., Alan L. Orvis, Ph.D., Donald A. Sones, M.D., and John W. Rosevear, M.D.

BENZOTHIADIAZINE ("thiazide") derivatives unquestionably are effective hypotensive agents, but the mechanism by which they reduce blood pressure has not been elucidated. Theories advanced to explain their hypotensive action include reduction of the volume of plasma and extracellular fluids, depletion of body sodium, other more obscure effects of diuresis, and a depressor effect unrelated to their known diuretic action.

This study was undertaken in an effort to acquire more information regarding possible mechanisms by which thiazide diuretics reduce the blood pressure of hypertensive patients.

Methods and Materials

A group of 28 hypertensive patients was included in this study; 19 were men, and the ages of the patients ranged from 36 to 75 years. All had sustained diastolic hypertension of mild to moderate severity. Only two had the retinal findings of group 3 hypertension;[1] the remainder had retinal arteriolar changes of group 2. None had congestive cardiac failure or detectable edema from any cause at the time the studies were made. Blood urea measured less than 50 mg. per 100 ml. before therapy with thiazide agents was started in all patients. No restriction of dietary sodium was imposed on any of the patients during these studies, and none received supplementary potassium.

The patients were chosen for this investigation on the basis of (1) their availability for repeated laboratory determinations during treatment, (2) adequate records of blood pressure before and during therapy, and (3) their expressed willingness to cooperate in this study. Twenty-one patients were residents of Rochester, Minnesota, or the immediate vicinity; of the remainder, three took their own blood pressure at home. Two patients had undergone previous sympathectomy.

The thiazide diuretics and the doses used in this investigation are listed in table 1. Nineteen patients did not receive any other antihypertensive agents, whereas eight were given additional antihypertensive agents at various intervals after use of the thiazide diuretic had been started; the remaining patient received pentolinium before and during treatment with thiazides. Except for this last case, no attempt was made to correlate changes in blood pressure with changes in plasma volume during periods when other antihypertensive drugs were employed, since the exact role of the diuretic could not be adequately assessed under such circumstances. The blood pressure always was determined while the patients were sitting.

One or more of the following laboratory determinations were done at least once before treatment and on one or more occasions during therapy with one of the thiazide diuretics: The total plasma volume was determined by injecting intravenously 18 ml. of a sterile 1.5 per cent solution of Congo red and determining the amount of dye in the plasma 5 minutes later.* Exchangeable sodium (Na_e) in the body was calculated from the specific activity of radiosodium (Na^{24}) in the serum as measured in a standard sodium iodide (thallium-activated) well-type scintillation counter 24 hours after the injection of a known quantity of this isotope. In four instances, the exchangeable potassium (K_e) in the body was calculated from the specific activity of radiopotassium (K^{42}) in urine as measured in a beta-sensitive, plastic, well-type scintillation counter 24 hours after the injection of a known quantity of this isotope. In one patient (case 10), K_e was calculated from the specific activity of K^{42} in the serum as measured in a standard scintillation counter. It is our opinion that determinations of K_e are more accurate when calculated from the specific activity of urine, but this method was not being used when the studies were made in case 10. The K^{42} and Na^{24} tracers were administered on consecutive days. Determinations of serum sodium and potassium were made on a flame photometer from Advanced Instruments, Incorporated; determinations of urinary sodium and potassium were made with a

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*These tests were performed by technicians in the Section of Clinical Pathology under the supervision of Dr. Don R. Mathieson.

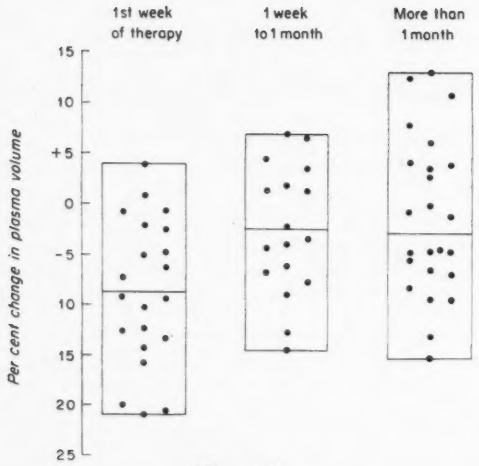

Figure 1

Effect of treatment with thiazide diuretics on plasma volume of 25 hypertensive patients. Values obtained during therapy were compared with pretreatment values for each patient to determine the percentage change. The transverse line in each bar represents the percentage change of the mean of the determinations during treatment from the mean of the control values.

Coleman flame photometer. Urinary aldosterone was determined by a modification[2] of the method of Neher and Wettstein.[3]

Results

Plasma Volume

A total of 62 determinations of plasma volume were made on 25 of these hypertensive patients from 3 days to 8½ months after use of a thiazide diuretic had been started. When determinations were repeated in the same period of observation, only the first measurement for each patient in each period was used for statistical analysis of paired data (table 2).

A statistically significant reduction in plasma volume occurred during the first week of therapy with thiazide diuretics (fig. 1). The average reduction during this period was 8.8 per cent. As treatment was continued, however, the plasma volume tended to return to or toward normal, and the modest reductions in mean plasma volume observed after the first week of therapy were not statistically significant.

Table 1

Thiazide Agents Used in 28 Hypertensive Patients

Diuretic and dose, mg./day		Patients
Chlorothiazide		11
	1000	5
	500–1000	2
	1000–1500	1
	250– 500	1
	500	1
	1500	1
Hydrochlorothiazide		13*
	75	1
	150	2
	100	9
	100–150	1
Trichlormethiazide		6*
	10	6

*Two patients received hydrochlorothiazide and trichlormethiazide at different periods during this investigation.

A correlation was apparent between the reduction in plasma volume and the reduction in mean blood pressure during the first week of diuretic therapy, but this was less evident in subsequent weeks (fig. 2).

Electrolytes

Determinations of the 24-hour Na_e and K_e, as well as serum levels and quantities of these electrolytes in 24-hour samples of urine, were made 11 times on five hypertensive patients during treatment with one of the thiazide diuretics, and the results were compared with the pretreatment values for each patient (table 3).

Sodium

No significant change from the control values was noted in the serum sodium or the 24-hour Na_e during the first 2 weeks of treatment or in subsequent weeks (fig. 3). However, urinary sodium was consistently and significantly greater during use of the diuretic agents, and this increase was evident throughout the periods of observation, which ranged from 2 to 8½ months.

Potassium

Four of the five patients exhibited some reduction of serum potassium during the first 2 weeks of treatment, the mean level during this period being 7.5 per cent below the mean

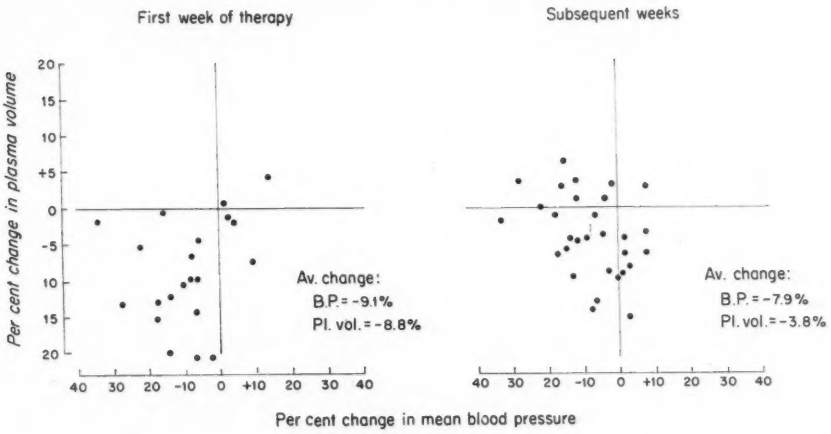

Figure 2

Relationship of changes in plasma volume to changes in mean blood pressure (systolic plus diastolic divided by 2) of 24 hypertensive patients treated with thiazide diuretics. Values obtained during treatment were compared to pretreatment values for each patient to determine the percentage changes shown here.

Table 2

Analysis of Paired Data on Effect of Thiazide Diuretics on Plasma Volume

		Period of observation after starting therapy		
		First week	1 Week to 1 month	More than 1 month
Number of patients (one determination per patient per period)		21	15	16
Mean plasma volume (ml.) and standard error	Before therapy	3049 ± 122	3021 ± 164	2950 ± 137
	During therapy	2780 ± 120	2960 ± 168	2911 ± 118
Mean of differences and standard error		−269 ± 51	−61 ± 47	−39 ± 58
P value (Student's "t test"		< 0.001	0.2 — 0.3	0.4 — 0.5

level before treatment was started (fig. 4). For only two patients (three determinations) was a reduction of serum potassium found during subsequent weeks of therapy. Values for 24-hour K_e were reduced in four of the five patients during the first 2 weeks of therapy, the mean value being 6.3 per cent less than the mean of pretreatment values. In subsequent weeks, the 24-hour K_e was greater than control values in four of six determinations, the increase in the mean value being 5.2 per cent. The quantity of potassium in random 24-hour collections of urine was greater than pretreatment values for all patients whenever it was determined.

Excretion of Aldosterone

Sixteen determinations of the quantity of aldosterone excreted in the urine in 24 hours were made on nine hypertensive patients from 3 days to 2 months after use of a thiazide diuretic was initiated. Almost all of the values were within normal limits (2 to 16 μg. per day) and did not vary significantly from pretreatment levels (table 4). In case 5 (table 4), the excretion of aldosterone increased from a level of 10 μg. per 24 hours before treatment

Table 3

Effect of Thiazide Diuretics on Sodium and Potassium in Serum, Urine, and Body Stores in Hypertension

Case	Drug*	Daily dose, mg.	Time after starting treatment	Average blood pressure, mm. Hg	Body weight, Kg.	Sodium				Potassium				Na_e/K_e
						Serum mEq./L.	24-Hr. exchange		Urine mEq./24 hr.	Serum, mEq./L.	24-Hr. exchange		Urine, mEq./24 hr.	
							Total mEq.	mEq./Kg.			Total mEq.	mEq./Kg.		
10	None	—	—	215/132	85.7	136	2992	34.9	122	3.9	2707	31.6	58	1.11
	C	1000	4 days	202/135	81.8	137	3041	37.2	140	2.9	2160	26.4	73	1.41
	C	500	8.5 mo.	142/100†	73.6	141	2940	39.9	160	4.3	3080	41.8	90	0.95
7	None	—	—	210/120	68.6	144	2840	41.4	138	3.7	2450	35.7	85	1.16
	H	75	12 days	155/100	66.4	133	2530	38.1	166	3.5	2170	32.7	90	1.17
	H	75	2 mo.	150/110	65.2	135	2630	40.3	179	3.6	2050	31.4	97	1.28
	H	75	6.5 mo.	165/104	65.9	147	2735	41.5	139	3.0	2410	36.6	115	1.13
8	None	—	—	188/138	85.5	140	3750	43.9	112	4.2	4060	47.5	69	0.92
	H	150	12 days	167/124	85.0	145	3900	45.9	204	3.7	3520	41.4	104	1.11
	H	150	2 mo.	127/104†	85.5	142	3840	44.9	281	4.4	3680	43.0	94	1.04
5	None	—	—	165/115	109.1	142	3860	35.4	150	4.4	3890	35.7	48	0.99
	None	—	—	165/110	105.7	129	3670	34.7	159	4.7	3850	36.4	43	0.95
	H	100	14 days	158/100	103.0	143	3700	35.9	167	4.3	3260	31.7	56	1.13
	H	100	2 mo.	165/110	101.8	145	3840	37.7	194	3.4	3830	37.6	65	1.00
11	None	—	—	195/152	89.5	143	3920	43.8	89	3.6	2800	31.3	42	1.40
	C	1500	5 days	175/126	87.7	143	3780	43.1	181	4.1	3380	38.5	107	1.12
	C	500	2.5 mo.	168/130	81.6	141	3680	45.1	208	4.2	3240	39.7	100	1.14
			Averages:											
			No treatment		87.3	140	3453	39.8	123	4.0	3177	36.4	60	1.09
			First 2 weeks		84.8	140	3390	40.0	172	3.7	2898	34.1	86	1.17
			Subsequent weeks		78.9	142	3277	41.6	193	3.8	3048	38.3	93	1.08

*C, chlorothiazide; H, hydrochlorothiazide.

†Receiving additional hypotensive agent.

to a distinctly abnormal level of 35 μg. per 24 hours 5 days after the use of hydrochlorothiazide was begun. Subsequent values in this case were normal, however. In four patients (cases 1, 5, 6, and 9), urinary aldosterone was within normal limits at times when diuretic therapy had reduced the plasma volume by more than 10 per cent. The reduction in plasma volume was less than 10 per cent when the urinary aldosterone was increased in case 5; later, when the value for urinary aldosterone had returned to normal, the reduction of plasma volume was even greater. Decreases in serum sodium and total Na_e were not attended by an increase in urinary aldosterone (case 7). Although reduction of serum potassium may have been responsible for inhibiting the secretion of aldosterone in four patients (cases 1, 3, 4, and 8), serum potassium was normal in the other four patients who failed to exhibit an increase in urinary excretion of aldosterone. In case 5, the value for serum potassium was actually low at the time the excretion of aldosterone was increased.

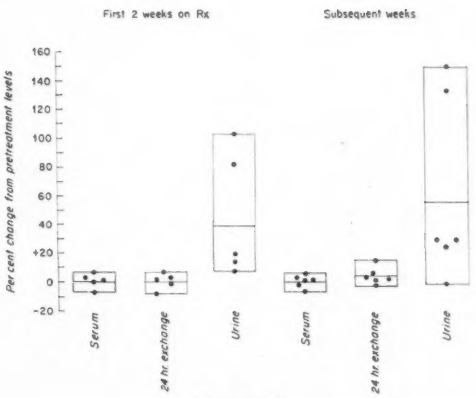

Figure 3

Effect of thiazide diuretics on sodium levels of five hypertensive patients. Each value was compared to pretreatment values in the same patient to determine the percentage change. Urinary values represent quantities of sodium excreted in random 24-hour samples collected as part of the determinations of Na_e. The percentage change in 24-hour Na_e was calculated on the basis of milliequivalents per kilogram of body weight rather than total milliequivalents. The transverse line in each bar represents the percentage change of the mean of the values obtained during treatment from the mean of the values before treatment.

Comment

Plasma Volume

Wilson and Freis[4] demonstrated that oral administration of chlorothiazide produced reductions in the volume of extracellular fluids and plasma, and they were the first to speculate that the hypotensive action of this drug could be explained on this basis. Others[5-7] also have demonstrated the hypovolemic effect of chlorothiazide during the first few days of treatment. However, observations made during prolonged use of chlorothiazide indicate that the initial reduction in plasma volume is temporary.[8-10]

The results of our study also indicate that this change is short-lived, because the initial reduction in plasma volume observed in our patients was less pronounced after the first week of therapy with a diuretic agent. The previous investigators reported longer intervals, probably because they did not repeat estimations of the plasma volume often enough during treatment to determine accurately the duration of this hypovolemic effect of thiazide agents. Our study apparently showed a correlation between reduced plasma volumes and a reduction in blood pressure during the first week of therapy with a thiazide drug; thereafter, however, the blood pressure remained at lower levels despite the fact that the plasma volume tended to return to or toward pretreatment levels. Therefore, a decrease in plasma volume cannot explain the prolonged hypotensive action of these agents.

The observation that the initial loss of body weight observed in four of five patients (table 3) persisted even though the plasma volume was reduced only temporarily is in accord with that of Lauwers and Conway,[10] who found that both body weight and total body water were decreased persistently and significantly by the administration of chlorothiazide and who postulated that this must result from intracellular dehydration.

Electrolytes

Our study failed to detect any significant depletion of body stores of sodium, as meas-

Table 4

Effect of Thiazide Diuretics on Excretion of Aldosterone in Hypertension

Case	Drug*	Daily dose, mg.	Time after starting treatment	Average blood pressure, mm. Hg	Urinary aldosterone, mcg./24 hr.	Plasma volume		Serum sodium		24-Hr. exchange sodium (Na_e)		Serum potassium		24-Hr. exchange potassium (K_e)		
						Ml.	Change, per cent	mEq./L.	Change, per cent	mEq./Kg.	Change, per cent	mEq./L.	Change, per cent	mEq./Kg.	Change, per cent	Na_e/K_e
1	None	—	—	160/102	10	3250						4.5				
	C	1000	3 days	150/100	11											
	C	1000	5 days	130/ 92	13	2833	−12.8					3.5	−22.2			
2	None	—	—	162/ 92	16											
	H	100	19 days	162/107	11											
3	None	—	—	180/103	6							4.5				
	H	100	11 days	135/ 75	5							3.5	−22.2			
4	None	—	—	157/ 80	3							4.6				
	H	150	17 days	184/ 90	6							3.7	−19.6			
5	None	—	—	165/115	10	4145		142		35.4		4.4		35.7		0.99
	H	100	5 days	165/105	35	3836	− 7.5					3.4	−22.7			
	H	100	14 days	158/100	9			143	+0.7	35.9	+1.4	4.3	− 2.3	31.7	−11.2	1.13
	H	100	2 mo.	165/110	13	3710	−10.5	145	+2.1	37.7	+6.2	3.4	−22.7	37.6	+ 5.3	1.00
6	None	—	—	164/102	9	3096						4.5				
	T	10	5 days	137/ 92	12	2713	−12.4					4.2	− 6.7			
	T	10	5 wk.	145/ 90	12	2955	− 4.6					4.1	− 8.9			
7	None	—	—	210/120	6	2760		144		41.4		3.7		35.7		1.16
	H	75	12 days	155/100	6	2809	+ 1.8	133	−7.6	38.1	−8.0	3.5	− 5.4	32.7	− 8.4	1.17
	H	75	2 mo.	150/110	8	2760	0.0	135	−6.2	40.3	−2.7	3.6	− 2.7	31.4	−12.0	1.28
8	None	—	—	188/138	20	2935		140		43.9		4.2		47.5		0.92
	H	150	12 days	167/124	19	3036	+ 3.4	145	+3.6	45.9	+4.6	3.7	−10.7	41.4	−12.8	1.11
	H	150	5 wk.	130/ 98†	0.6	3110	+ 6.0					3.3	−21.4			
9	None	—	—	182/115	0.8	2281						3.9				
	H	100	4 days	164/110	6	1962	−14.0					4.1	+ 5.1			
	H	100	3 wk.	150/100	3	2142	− 6.1					3.7	− 5.1			

*C, chlorothiazide; H, hydrochlorothiazide; T, trichlormethiazide.

†Receiving additional hypotensive agent.

ured by the isotope-dilution technic, either early or late in the course of treatment.

Our findings, as well as those of others[10–13] who have not found any consistent change in body stores of sodium, indicate that chronic depletion of body sodium does not occur and is, therefore, not a satisfactory explanation for the hypotensive effect of thiazide diuretics.

As already noted, a reduction in the 24-hour K_e took place in four of five patients during the first 2 weeks of therapy with a thiazide diuretic, but the values thereafter reverted to or toward pretreatment levels.

An interesting observation incidental to the determination of Na_e and K_e was the consistently increased quantity of sodium and potassium in 24-hour specimens of urine obtained at intervals throughout the period of treatment with diuretics. The fact that this occurred without measurable depletion of the body stores of these electrolytes suggests that (1) the patients increased their intake of sodium and potassium, or (2) there was increased absorption or decreased excretion of these electrolytes from the gastrointestinal tract, or (3) both events occurred. It is extremely doubtful that if all the sodium and potassium normally excreted in the intestinal tract were diverted to the urine it could account for the rather large increases in urinary excretion observed in this study. On the other hand, if these patients did increase their consumption of these electrolytes, it was done subconsciously, for they denied any change of dietary habits when questioned directly about this. It should be emphasized, however, that these were not balance studies, for no attempt was made to measure or restrict the dietary intake of sodium and potassium.

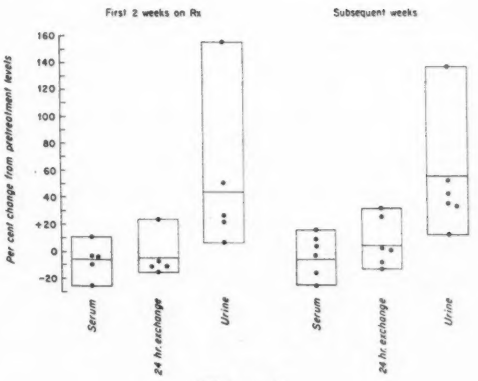

Figure 4

Effect of thiazide diuretics on potassium levels of five hypertensive patients. Each value was compared to pretreatment values in the same patient to determine the percentage change. Urinary values represent quantities of potassium excreted in random 24-hour samples collected as part of the determinations of K_e. The percentage change in 24-hour K_e was calculated on the basis of milliequivalents per kilogram rather than total milliequivalents. The transverse line in each bar represents the percentage change of the mean of the values obtained during treatment from the mean of the pretreatment values.

Excretion of Aldosterone

Although Freis,[14] as well as Hollander and associates,[15] has speculated that prolonged use of thiazide diuretics might induce a state of secondary hyperaldosteronism, and Barter and co-workers[16] have shown that the administration of mercurial diuretics is followed by an increase of urinary aldosterone, we found nothing in the literature to indicate that actual measurements of urinary aldosterone have been made in a series of nonedematous hypertensive patients who were receiving thiazide diuretics. Our study demonstrated no increase in the excretion of aldosterone in eight of nine patients who were receiving these agents; a temporary increase occurred in one case. The excretion of aldosterone remained normal in these patients despite the fact that hypovolemia and a reduction in serum sodium, stimuli that have been shown to increase the adrenal secretion of this hormone,[16–19] were present in some. It may be that the concomitant reduction in serum potassium may have had an inhibitory effect on the adrenal secretion of aldosterone,[17, 20] although table 4 reveals that urinary aldosterone remained normal in some cases even though serum potassium was not depressed, and that the isolated increase of urinary aldosterone in case 5 occurred despite moderate hypopotassemia. Whatever the reason, we found no evidence that prolonged treatment with thiazide diuretics induces

*C, chlorothiazide; H, hydrochlorothiazide; †Receiving additional hypotensive agent.

secondary hyperaldosteronism, insofar as this condition can be measured by urinary excretion of aldosterone.

Possible Mechanism of Hypotensive Action of Thiazides

Our original purpose in undertaking this investigation was to elucidate, if possible, the mechanism by which thiazide diuretics act in reducing blood pressure. Our evidence indicates that the chronic hypotensive action of these drugs does not result from reduction in plasma volume or from depletion of body stores of sodium, yet we have not satisfactorily explained their hypotensive action. One might be tempted to speculate that this effect is independent of their diuretic properties, but the facts that all potent diuretics are also hypotensive agents and that the magnitude of their hypotensive action bears a direct relationship to their diuretic potency make plausible the theory that the hypotensive effect of diuretics must be related intimately in some way to their diuretic activity. In the light of present knowledge, one could postulate that the hypotensive action of diuretic agents results from enhanced excretion of some unidentified pressor substance or trace metal[21] or from an internal redistribution of water and sodium within the organism without detectable net losses of the latter. Perhaps the ratio of extracellular sodium to intracellular sodium[22] is changed in a beneficial way, or perhaps the arterial wall is depleted of the excessive stores of sodium and water that Tobian and Binion[23] have demonstrated in hypertensive humans and animals.

Summary

A study has been made at the Mayo Clinic of the results of treatment in 28 hypertensive patients receiving thiazide diuretics. The use of these agents produced a significant but very temporary reduction in plasma volume in most patients. The plasma volume reverted to or toward normal after the first week of treatment; therefore, hypovolemia could not explain the prolonged hypotensive effect of these drugs. Administration of thiazide diuretics did not deplete the body of its sodium stores, as measured by isotope studies in five patients on an unrestricted diet. Therapy with thiazides did not produce a persistent increase in urinary aldosterone excretion in the nine patients studied for this possibility.

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On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves

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. . . the hypertrophy is recognized as a provision of nature to make the power of the part equal to the obstacle it has to overcome; and yet this simple principle seems to have been entirely overlooked in diseases of the heart, as if this organ possessed muscular fibres of a different nature from other organs, or as if, in adapting itself to obstacles affecting its action, it follows laws different from other muscular parts. The consequency of the neglect of this principle has been, that too often, in treatment of a valvular alteration in the heart, there has been a constant struggle between nature and medicine. Nature has been making the organ equal to its task; while medicine has been directed to counteract nature's efforts, and, by weakening the organ, to render it totally incapable of its task. The repeated bleedings, the starvings, the enforcement of debilitating measures, are totally unsuited to the disease we are considering.

Thrombelastographic Studies with a Twenty-Four-Hour Schedule for Subcutaneous Heparin

A Comparison of Its Efficiency with Prothrombin-Depressing Agents

By ROBERT S. ELIOT, M.D., KURT N. VON KAULLA, M.D., AND S. GILBERT BLOUNT, JR., M.D.

THESE STUDIES were designed to explore the feasibility of a single daily heparin injection as anticoagulant therapy, with the possibility of self-treatment on an outpatient basis in mind. The effects of therapy on the over-all coagulation of blood as measured with the thrombelastograph were compared with those obtained by prothrombin-depressing agents.

The need of a form of anticoagulant therapy for use by physicians having poor facilities for prothrombin determination induced us to re-evaluate heparin as a long-term anticoagulant. The undesirable side effects of prothrombin-depressing agents in some patients, and the availability of a concentrated heparin suitable for subcutaneous injection were also factors leading to the initiation of this study.

Materials and Methods

Anticoagulants

Aqueous Sodium Heparin 40 per cent (400 mg./ml.)* was used throughout. Dicumarol and coumadin were used as prothrombin-depressing agents.

Heparin was injected into the subcutaneous fat above the iliac crest with a 5/8-inch 25-gage needle and a 40-unit insulin syringe. The heparin dosage was read directly from this syringe. For example, a 72-Kg. patient received a heparin dosage of 4.5 mg./Kg., or 324 mg., which for a 40 per cent heparin solution (400 mg./ml.) corresponded to 32.4 units on the syringe.

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*Lipo-Hepin Darwin products of Riker Labs, Inc., Northridge, California.

Patients

Five groups of patients were included in this study: (1) convalescent patients with no thromboembolic disease who had received various amounts of subcutaneous heparin in order to establish the optimal dosage for 24-hour anticoagulation; (2) patients with no thromboembolic disease who had received a single dose of subcutaneous heparin sufficient for 24-hour anticoagulation; (3) patients with or without thromboembolic disease who had received a single daily dose of subcutaneous heparin sufficient for 24-hour anticoagulation for five to seven days; (4) patients with thromboembolic disorders treated with a single daily subcutaneous heparin injection for a period of 1 week to several months, either in the hospital or on an outpatient basis; and (5) control patients with thromboembolic disease treated with Dicumarol or coumadin.

Control of the Anticoagulant Action

The Hartert-thrombelastograph[1] was used throughout the study. This instrument was selected because it registers completely the kinetics of fibrin clot formation and produces a permanent record. It also records the firmness of the clot formed. At this investigational phase of the study of the action of subcutaneous heparin on the "clotting time" the continuous recording of the entire fibrin formation was the logical measurement of the "clotting time," since coagulation is a continuous process and there is no such thing as a true "clotting time." The conventional clotting times are purely relative and arbitrarily chosen points on the clotting curve. They would not provide basic information on the effect of subcutaneous heparin on the over-all clotting process. The thrombelastographic data used for the evaluations and final calculations were the "reaction" time, the time from recalcification to the appearance of the first measurable fibrin strand and "5 mm." time, the time from recalcification until the coagulogram (thrombelastogram) had reached a broadness of 5 mm. (until the clot had developed about 10 per cent of the firmness of a normal clot). The "5 mm." time is less than the "20 mm." time used by other investigators,[2] for the delayed and inhibited clotting action obtained

with effective heparinization made the "20 mm." time impractical. The film speed of the thrombelastograph in these studies was reduced to 1 mm. per minute from the 2 mm. per minute ordinarily used.

Blood was drawn with a two-syringe technic. The first syringe was discarded and the second, containing 2 ml. of sodium citrate U.S.P. 3.8 per cent, was filled to 10 ml. The blood and citrate were carefully mixed immediately and then centrifuged at 1,500 g. for 5 minutes. Thirty-three hundredths of a millimeter of the plasma was placed in a cup of the prewarmed thrombelastograph and recalcified with 0.03 ml. of 0.5 M calcium chloride. The Lee-White clotting time was also checked in some patients. When this was done, the blood was drawn in three syringes. The first syringe was again discarded, the second one was used for the Lee-White clotting time, and the third was used for the thrombelastographic tests. In patients treated with prothrombin-depressant agents, prothrombin time, isolated prothrombin, and proconvertin were determined by conventional methods. Citrated plasma, rather than whole blood, had to be used with the thrombelastograph, since blood samples were obtained from patients at two different hospitals and were brought to the laboratory for processing. It was possible, however, to start the test within 20 minutes after the blood was drawn.

Control samples of blood were drawn from all patients who were to be treated with heparin. After the heparin injection, serial samples were drawn at various times to establish the onset and duration of the heparin action.

Results

Onset of Heparin Action (Heparin Absorption)

Serial coagulation studies made after an injection of concentrated heparin into the subcutaneous fat revealed that sufficient heparin had been absorbed in most patients within the first hour and in all within 2 hours to bring about a clear-cut prolongation of the "reaction" time. After a subcutaneous injection of 50 mg. of heparin, a very marked prolongation of the "reaction" time, with concomitant pronounced prolongation of the "5 mm." time, was obtained in 2 hours (fig. 1). The heparin absorption that induced a maximum anticoagulation was obtained in some instances later than 2 hours after injection. Two hours after a subcutaneous injection of 4 mg./Kg. of heparin, there was some prolongation of the "reaction" time and the "5 mm." time; 4 hours after injection, both times became greatly prolonged.

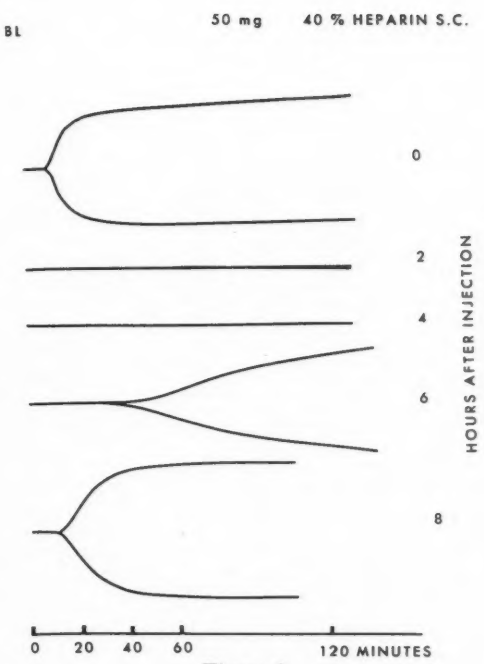

Figure 1

Serial coagulograms (thrombelastograms) after subcutaneous injection of 50 mg. of 40 per cent heparin. Time scale on bottom for "reaction" times.

Duration of Heparin Action

The duration of the anticoagulant action of subcutaneous heparin depends upon the dosage employed. The anticoagulant action of 50 mg. did not last longer than 8 hours (fig. 1). A dosage of 3.5 to 4.5 mg./Kg. was adequate in most patients to obtain a clear-cut anticoagulation from 20 to 24 hours. It was not possible, however, to establish a general rule for the exact dosage, which had to be determined for the individual patient. Figure 2 shows serial coagulograms of a patient who received a subcutaneous injection of 4 mg./Kg. of heparin. Prolongation of the "reaction" time became very evident after 4, 6, and 8 hours after injection and was still prolonged to about three times the control value at 13 and 18 hours; some prolongation was

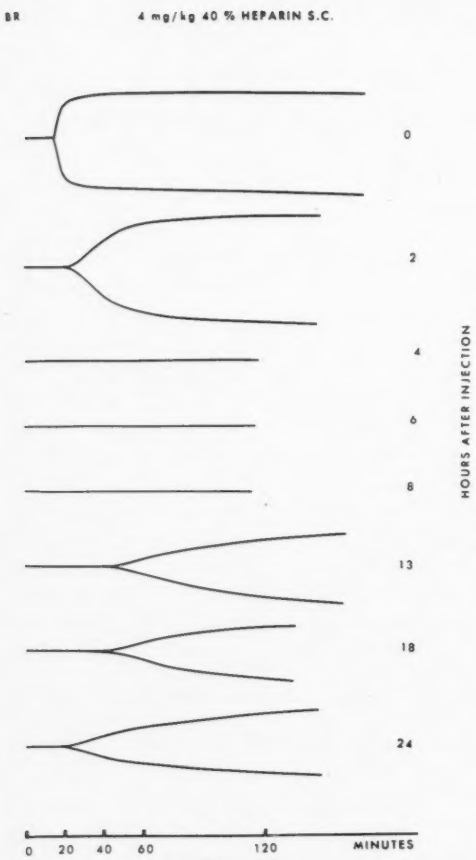

Figure 2

Serial coagulograms (thrombelastograms) after subcutaneous injection of 4 mg./Kg. 40 per cent heparin. There was some inhibition of coagulation at 2 hours, complete anticoagulation at 4 hours, a gradual return toward normal values at 16 hours, and still some anticoagulant effect left after 24 hours. Time scale on bottom for "reaction" times.

still demonstrable at 24 hours. The "5 mm." time followed a corresponding trend. Figure 3 provides some additional examples of the duration of action of subcutaneous heparin.

Establishment of Adequate Dosage

In pilot experiments the anticoagulant action of 4 mg./Kg. of subcutaneous 40 per cent heparin was found to last at least 20 hours in the average patient. Consequently, the initial dose of heparin given to patients was 4 mg./Kg. unless they were patients who had recurrent thrombosis or embolism or exhibited clotting features (prothrombin activity above 100 per cent, accelerated thrombin generation, marked shortening of reaction time, or 5 mm. time, or both, in the coagulogram)[3, 4] that might be interpreted as signs of hypercoagulability; these patients received from 4.5 to 5.5 mm./Kg. as an initial dose. Whenever possible, the treatment was started at 4:00 p.m. The coagulation was checked after 16, 20, and 24 hours (8:00 a.m., 4:00 p.m., 12:00 noon, and the next day). From these tests we established the optimal dosage for the second and subsequent injections. An attempt was made to obtain marked anticoagulation at 20 hours ("reaction" time, prolonged but less than twice of normal), as shown in figure 3. We found it unnecessary to repeat the 16-, 20-, and 24-hour checks every day. Further tests during the course of the treatment were made at 20 hours after injection; daily during the first few days of the treatment, then twice weekly, and finally once a week. The results shown in figure 3 were obtained several weeks to several months after the start of the treatment. The tests were made during routine weekly 20-hour control checks. The 16- and 24-hour tests shown in figure 3 were made for demonstration purposes only.

When a marked heparin effect was observed at 24 hours, the determination was again repeated at 20 hours after another injection with the same heparin dose. If the reaction time then was longer than 60 minutes, the heparin dose was decreased by 10 per cent. Similarly, the heparin dose was raised 10 per cent if anticoagulation was not clear-cut at 20 hours.

The measurement of the "reaction" time alone does not reflect the entire clotting situation. Under the heparin action, the fibrin formation proceeds at a reduced rate, indicated by the slowly increasing broadness of the coagulogram figures 1, 2, and 3 as compared with normal coagulograms, resulting in a very prolonged "5 mm." time. Thus, heparin delays both the onset and the progress of fibrin formation.

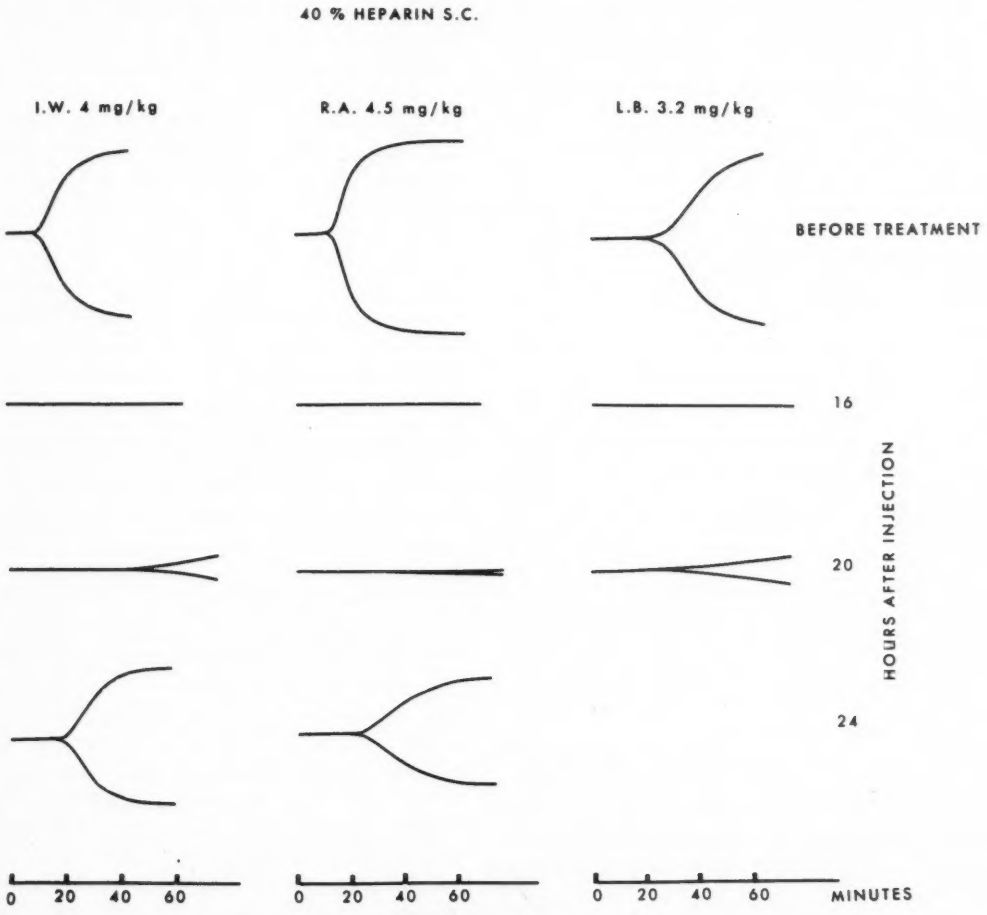

Figure 3

Serial coagulograms (thrombelastograms) obtained 16, 20, and 24 hours after subcutaneous injection. Tests were done several months after start of treatment. There was complete inhibition of coagulation at 16 hours, marked inhibition at 20 hours, and minor inhibition at 24 hours after injection. Time scale on bottom for "reaction" times.

Case Histories

I.W. is a 72-year-old white man who had experienced an acute myocardial infarction 4 weeks prior to his admission to C.G.H. The single complication was bilateral femoral thrombophlebitis occurring 2 days prior to his admission. He was treated with coumadin, bedrest, and local heat therapy. The phlebitis began to disappear but gross urinary tract bleeding developed in the absence of demonstrable disease of the genitourinary system. His prothrombin activity was then between 12 and 25 per cent of normal. Coumadin was gradually discontinued, but the phlebitis recurred, and pulmonary infarct followed. Subcutaneous heparin injections were then started once every 24 hours. The phlebitis disappeared within 7 days. The patient was discharged but maintained himself on a heparin dosage of 4 mg./Kg. per day. One 10 per cent increase in the dosage was necessary. He has been followed as an outpatient for 7 months without a recurrence of phlebitis and without bleeding. This patient urgently needed anticoagulant therapy but could not tolerate coumadin because of localized capillary

bleeding. Successful anticoagulation was effected with heparin without bleeding. The coagulograms made before the start of treatment and 5 months later (16-, 20-, and 24-hour checks) are reproduced in figure 3.

R.A. is a 61-year-old man who had had a myocardial infarction complicated by pulmonary infarction and congestive failure. He was given subcutaneous heparin therapy with a dosage of 4.5 mg./Kg. daily and discharged from the hospital after 4 weeks' convalescence. He has been continued as an outpatient for 3 months without complication on heparin therapy. There have been no recurrent pulmonary nor myocardial infarcts and no bleeding complications. The coagulograms made before treatment and 6 weeks later (16-, 20-, and 24-hour checks) are reproduced in figure 3.

L.B. is a 27-year-old white man who experienced an uncomplicated myocardial infarction. Stable control was not possible after 2 months of attempted coumadin therapy. The patient bled on two occasions from his urinary tract, and the drug was finally discontinued. No urinary tract infection was found. He gave himself subcutaneous heparin in a dosage of 3.5 mg./Kg. for 4 months on an outpatient basis, and his control since then has been stable and uncomplicated. The coagulograms made before the beginning of treatment and at 12 weeks (16- and 20-hour checks) are also reproduced in figure 3.

The anticoagulant therapy was evaluated in all these patients once a week, 20 hours after a daily subcutaneous injection of heparin.

Comparison of the Anticoagulant Action of Subcutaneous Heparin with Prothrombin-Depressing Agents

Four characteristic thrombelastograms of patients treated with Dicumarol or with coumadin are shown in figure 4 for comparison with the action of subcutaneous concentrated heparin on the "reaction" time and the "5 mm." time. In all four patients, the prothrombin activity according to the one-stage prothrombin time was below 20 per cent and the proconvertin activity was below 17 per cent of the normal. Comparison of these coagulograms with the coagulograms (figs. 1, 2, and 3) obtained after subcutaneous injections of concentrated heparin, shows that the deviation from the normal in the coagulogram patterns of the patients treated with Dicumarol or coumadin are small. This observation reflecting a poor effect of prothrombin-depressing agents on the thrombelastogram has been made by other investigators.[5] Some of them demonstrate that the additional use of the thrombelastograph in the determination of the activity of the prothrombin complex is decisive for the prevention of failures of treatment with the prothrombin-depressing agents.[4] This poor effect indicates that the anticoagulation produced by prothrombin-depressing agents, as measured by the thrombelastographic recording of the over-all clotting process, is not nearly so complete as that from the subcutaneous injection of concentrated heparin. The fundamental differences between the anticoagulant effects of subcutaneous heparin and those of prothrombin-depressing agents become even more evident when the frequency distribution of the coagulogram values are tabulated (fig. 5). All patients receiving heparin represented in this figure were treated with an individually adjusted 24-hour heparin dose ranging from 3.5 to 4.5 mg./Kg.

Row A of histograms shows the distribution of the "reaction" times and the "5 mm." times of control coagulograms obtained before heparin administration (computed from 55 determinations). It can be seen that 95 per cent of the control values for the "reaction" times are less than 16 minutes and 90 per cent of the "5 mm." time values are less than 21 minutes. As shown in row B, all 22 patients treated with prothrombin-depressing agents were within the so-called therapeutic range of 15 to 20 per cent prothrombin activity. Fifty per cent exhibited reaction times within the 95 per cent range of the normal values and 41 per cent within the normal range for the "5 mm." time. The picture changes drastically on considering the "reaction" times obtained 16, 20, and 24 hours after the subcutaneous heparin. After 16 hours (row C), only 11 per cent of the values fell in the 95 per cent range of the normal values, while 76 per cent showed a very strong anticoagulation, which was noted in only 5 per cent of the patients treated with prothrombin-depressing agents. At 20 hours after heparin (row D) nearly 62 per cent of

the "reaction" times were outside the 95 per cent range of normal values and 34 per cent indicated a very marked anticoagulant effect (computed from 106 determinations). The 24-hour values (row E, computed from 55 determinations) indicated that 70 per cent of the "reaction" time values had returned to within the 95 per cent range of the normal values. For the "5 mm." times after 16 hours only 9 per cent had returned to the 90 per cent range of normal values while 78 per cent revealed a very strong anticoagulation. Twenty hours later 34 per cent had returned to the normal range and 37 per cent still showed a strong anticoagulation, and at 24 hours 55 per cent had returned to the normal range while 8 per cent continued to show a strong anticoagulation.

The fact that 70 per cent of the "reaction" times while only 55 per cent of the "5 mm." times had returned to the normal ranges after 24 hours indicates that the "5 mm." time is a more sensitive indicator of residual heparin action than the "reaction" time alone. In 8 per cent of the instances there was still a very marked anticoagulation after 24 hours ("reaction" time of more than 60 minutes).

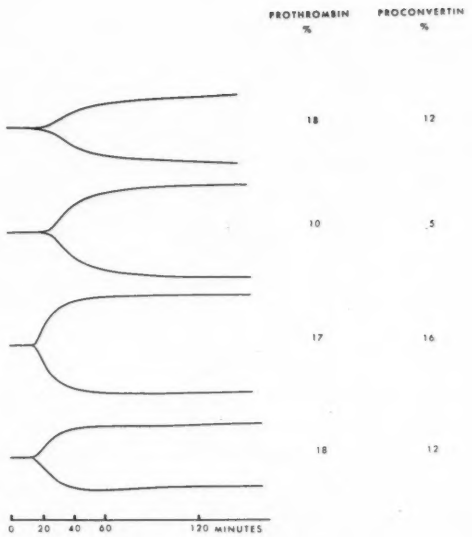

Figure 4

Coagulograms (thrombelastograms) of four patients treated with prothrombin-depressing agents. Treatment was instituted several weeks prior to test. Coagulograms were only moderately influenced by prothrombin-depressing agents at the "therapeutic" level. Time scale on bottom for "reaction" times.

Comparison of the Thrombelastographic Coagulograms with Other Control Technics

In a number of patients, parallel studies were done with the thrombin time, Lee-White time, and our modification of the recalcification time. These studies are not completed, but the thrombin time proved to be inadequate in following this form of heparin therapy. The values of the Lee-White time did reflect somewhat the trend seen with the thrombelastograph. The best results so far were obtained with our modification of the recalcification time. This procedure, in contrast to the Howell time, avoids a dilution of the plasma.[6] The clotting times obtained by this technic of the recalcification time corresponded in minutes roughly to reaction time plus "5 mm." time of the thrombelastographic coagulograms. Further studies will have to be made in order to substantiate this relation and the usefulness of the recalcification time. This method would certainly simplify the control of heparin-treated patients, because the tests, to some extent, could be done when convenient after the drawing of blood.

Precautions

It is very important that the heparin solution be injected into the subcutaneous fat, not into skin or muscle. A 25-gage or smaller needle should be used, and there should be no heparin drop visible on the needle tip when it penetrates the skin. Larger needles will invariably produce, sooner or later, a large hematoma. In general, the subcutaneous heparin should be injected at a site that is not subjected to any pressure or friction. The subcutaneous injection of concentrated heparin is painless in contrast to heparin in a menstruum.

One local allergic reaction was seen with itching and swelling, redness and heat of skin,

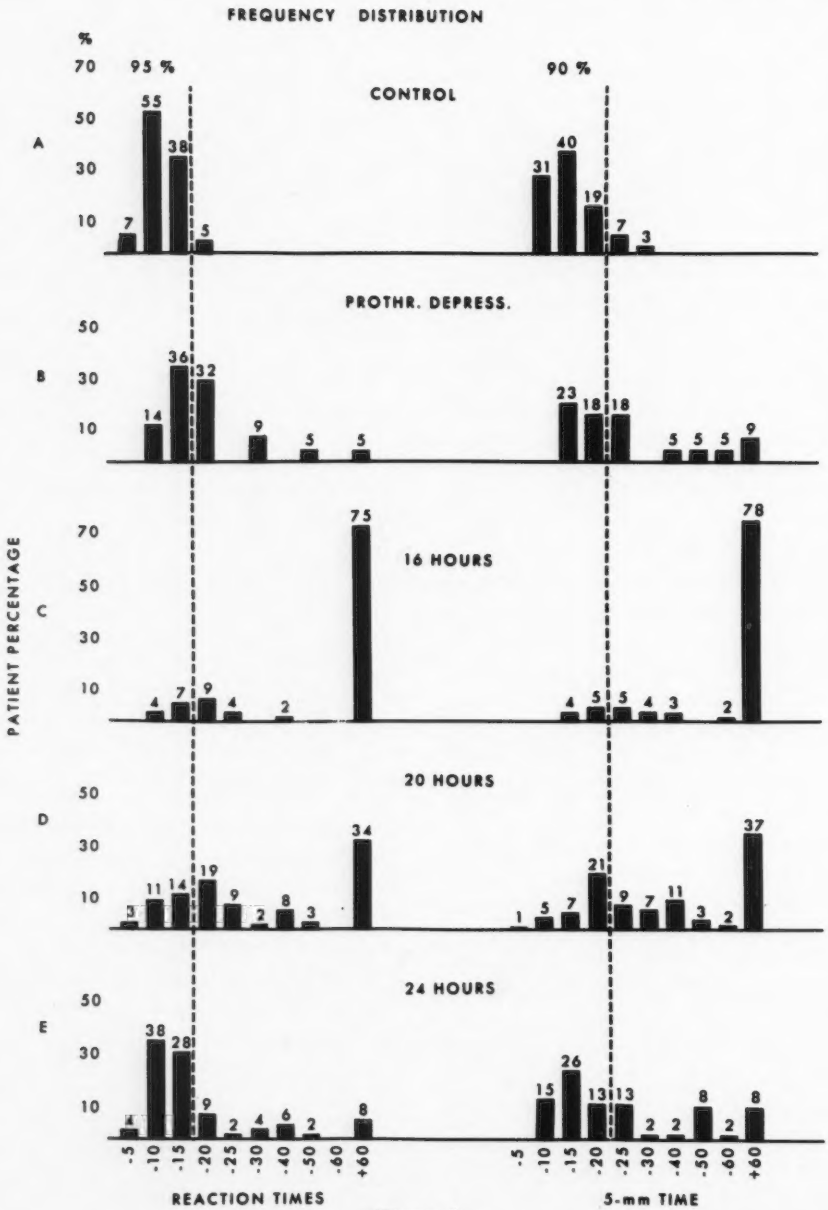

Figure 5

Frequency distribution of "reaction" times and "5 mm." times in patients before and during treatment with prothrombin-depressing agents and with heparin. A, *before treatment;* B, *during treatment with prothrombin-depressing agents;* C, *16 hours after subcutaneous aqueous concentrated heparin;* D, *20 hours after heparin;* E, *24 hours after heparin. Scale on the left side: percentage of patients whose "reaction" times and "5 mm." times were within each time period. Ninety-five per cent of the normal values for "reaction" time and 90 per cent of the normal values of the "5 mm." time fall into the range to the left side of the dotted lines.*

and ecchymosis. After a change to another brand of heparin, the reaction disappeared. One large-sized hematoma was observed at the site of heparin injection in a patient who received his injection during a fibrinolytic phase after an infusion of thrombolysin. Therefore, it might be advisable to treat patients during a fibrinolytic phase with smaller amounts of intravenous heparin if such treatment is needed.

Discussion

One major problem arising from the use of prothrombin-depressing agents is that of control. The clinician bases his therapeutic dosage upon the prothrombin time (the measurement of but one clotting parameter), confident that this is an indication of the degree of anticoagulation. Evidently, it does not reflect the true degree of anticoagulation. This has been recognized and a variety of modifications of the prothrombin time determination have been designed to avoid this deficiency. It has also been recommended that there should be a determination of additional clotting factors like proconvertin or Stuart-Prower factor.[7] The control of prothrombin-depressing agents may become more effective by these procedures, but it also becomes more complicated. In all patients whose coagulograms are shown in figure 4, proconvertin activity was below 17 per cent and yet the coagulograms did not show a significant reduction of the over-all coagulability nor any significant delay in clot formation. The histograms (row B fig. 5) indicate that about 50 per cent of patients who maintain a "therapeutic" level with prothrombin-depressing agents do not exhibit a significant reduction of the over-all coagulability. Any condition that increases the coagulability of their blood might possibly induce another episode of intravascular clotting.

It has been observed[8] by the use of the thrombelastograph that clear-cut phases of hypercoagulability followed by thromboembolic accidents do occur during "adequate" treatment with prothrombin-depressing agents. Such phases are not reflected by a shortening of the conventional prothrombin time, which remains within the "therapeutic" range. The hypercoagulability phases are thought to be caused by reactive hyperfibrinogenemia, increase in platelet activity, and other factors.[4]

In addition, patients treated within the therapeutic range with prothrombin-depressing agents may have bleeding problems. For this reason, this type of therapy had to be discontinued in two of our patients. The same two patients did not show any signs of bleeding when treated for months with a heparin dosage that induced a very marked degree of anticoagulation. Also, in patients treated with heparin we have never observed the erratic changes in responsiveness that are seen not infrequently during treatment with prothrombin-depressing agents.

From the data of the thrombelastographic studies presented in this paper it is concluded that the prothrombin-depressing agents reduce the over-all coagulability of the blood to a very limited extent. This opinion has been expressed by others.[4] These agents bring about a disturbance of clotting factors that does not, however, necessarily reduce the speed of fibrin formation or of the amount of fibrin formed. This is also indicated by the very fact that prothrombin-depressing agents do not affect sufficiently the clotting time so that it can be used as a laboratory control for these agents. Administration of sufficient amounts of these agents to prolong the clotting time to ranges comparable to those obtained after heparin injections leads to prominent toxicity. In contrast, the subcutaneous injection of concentrated heparin brings about an appreciable and lasting effect on the over-all coagulability of the blood without adverse reactions. Heparin has several further advantages over prothrombin-depressing agents: its anticoagulant action appears more rapidly, whatever form of injection is used; it does not depress liver function; its capillary toxicity is minimal; heparin is not retained in the body for days, but is quickly metabolized and excreted; heparin possesses a clearing activity in lipemia; and the clinical control of the effects of heparin on blood coagulation is less complicated.

The studies were carried out by thrombelastographic continuous recordings of the clotting, or, more correctly, the fibrin-formation process. The outcome of the fibrin formation as the result of the interaction of clotting factors is decisive in terms of biological effectiveness of any anticoagulant treatment. Thrombelastography, which is the best method available free of subjective errors, is to measure and record this process.[9] The reported retarding effect of treatment with a "once a day" schedule of concentrated subcutaneous heparin on the process of fibrin formation observed in serial blood samples obtained after injection is very encouraging and warrants further extended studies with the use of simpler technics (recalcification time, Lee-White time). Anticoagulant therapy with subcutaneous heparin controlled with appropriate methods would be indicated in all those situations in which a clear-cut and marked anticoagulant effect is desirable.

Subcutaneous heparin could also be considered for those patients who are already receiving prothrombin-depressing agents but demonstrate a bleeding tendency, thromboembolism, or other complications. Patients may readily be taught to treat themselves. Subcutaneous heparin given once a day would permit the patient to continue heparin therapy for much longer periods than with intravenous injection. With the proper spacing of the injection sites, the subcutaneous heparin injections could be carried on for months.

Summary

In 55 patients 430 thrombelastographic studies after 305 heparin injections revealed that a more complete and more rapid reduction of the over-all coagulability of the blood is obtained by a subcutaneous injection of 40 per cent heparin once every 24 hours than that obtained with prothrombin-depressing agents. The individual dose, by the thrombelastographic technic, is between 3.5 and 4.5 mg./Kg.

Further clinical studies are indicated with use of simple laboratory control technics, such as recalcification time.

Acknowledgment

We should like to express our appreciation to Thad Sears, M.D., Chief of Medicine at the Denver Veterans Administration Hospital. We should also like to thank Mrs. K. N. von Kaulla and Michael Gonzales for their technical aid.

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Simultaneous Determination of Temperatures of Skin and Muscle before and after Lumbar Sympathectomy

By HERBERT A. ROEDLING, M.D., GRACE M. ROTH, PH.D., COLLIN S. MACCARTY, M.D., AND RICHARD M. SHICK, M.D.

A CONTROVERSY has existed for many years as to whether sympathetic denervation of the lower extremities increases the circulation in the skin by shunting the flow of blood from the muscle to the skin. This action was suggested by Bierman[1] in 1941 after studies of the temperature of muscles in the lower extremities after lumbar sympathectomy. Under these circumstances one might postulate that a sympathectomy would not effectively increase the flow of blood* in an extremity or aid in the development of collateral circulation.

This study was undertaken to investigate, under rigid measures of control, simultaneous changes in the temperature of skin and muscle before and after sympathectomy, together with the sweating patterns of patients who have peripheral arterial disease.

Method

Skin Temperatures

All drugs were withheld for at least 12 hours before the test. The procedures used in determining temperatures of the skin and muscle were as follows. The patient fasted for 15 hours before the test. During the test he wore lightweight short pajamas and was in a supine position on a comfortable bed in a room with a constant air temperature of 25 C. and a relative humidity of 40 per cent. The basal blood pressure, pulse rate, and metabolic rate were determined.

Muscle and Skin Temperatures

The patient, previously lying on his back, turned on his stomach for 10 to 15 minutes and a thermo-electric needle† 5 cm. long and 1.2 mm. in diameter was inserted into the calf muscle of the extremity. The depth of the tip of the needle from the surface of the skin was at least 2.5 to 3 cm. A skin thermocouple was placed over the region adjacent to the thermo-electric needle. Simultaneous measurements of the temperature of the skin, meaning that of the calf, as well as the intramuscular temperature of the gastrocnemius muscle, were recorded at intervals of 2 minutes over a period of 20 minutes. The pulse rate and blood pressure were observed every 5 minutes.

Sweating Test

The cobaltous chloride procedure of one of us (Roth,[2] 1935) was employed to determine sweating activity. Cobaltous chloride in a saturated solution of 95 per cent ethyl alcohol is deep blue, but changes to a bright pink in the presence of water. This solution was applied in stripes on the anterior and lateral aspects of the head, trunk, and extremities. An aluminum heating cabinet containing a series of incandescent light bulbs to maintain a temperature of about 140 F., and large enough to cover the entire body except for the head, was placed over the patient. After 10 to 20 minutes of heating in this cabinet, thermoregulatory sweating was induced, and the stripes of cobaltous chloride were transformed to the characteristic bright pink in the presence of perspiration. The relative change in color of the stripes indicated the varying degrees of sweating with a considerable degree of accuracy. Anhidrosis of course was indicated by the persistence of deep blue. In the normal person sweating is fairly even and diffuse over all portions of the body.

Results

Twenty-six patients were studied before and after unilateral lumbar sympathectomy. Fourteen patients had undergone chemical sympathectomy (injection of 3 or 4 ml. of absolute alcohol in the sympathetic chain at the level of the bodies of the second and third lumbar vertebrae) and 12 patients had undergone surgical removal of the first, second and third or second and third lumbar ganglia on one side.

The average age of the 26 patients was 59 years, and the range was 21 to 78 years. If the two patients 21 and 30 years old are

From the Mayo Clinic and the Mayo Foundation, Rochester, Minnesota.

*Route of blood flow and the question of an effective increase of blood flow under these circumstances have not yet been determined in man.

†Electrolaboriet, Copenhagen, Denmark.

Table 1

Temperatures before and after Unilateral Lumbar Sympathectomy in Occlusive Arterial Disease: Group 1

Case	Age, sex,	Presympathectomy BMR	Presympathectomy Temperature, °C. Air	Presympathectomy Temperature, °C. Sural Muscle	Presympathectomy Temperature, °C. Sural Skin	Postsympathectomy BMR	Postsympathectomy Temperature, °C. Air	Postsympathectomy Temperature, °C. Sural Muscle	Postsympathectomy Temperature, °C. Sural Skin	Differences Muscle	Differences Skin	Sweating pattern
1	63 M	+ 4	26	32	31	+ 4	26	34	32	+2	+1	I*
2	39 M	−12	26	33	31	−12	25	35	33	+2	+2	I*
3	66 M	0	26	35	32	− 3	26	36	33	+1	+1	II
4	21 F	− 2	26	34	32	+ 1	25	36	33	+2	+1	II*
5	48 M	+ 4	25	34	31	+ 4	25	35	33	+1	+2	I*
6	57 F	− 2	25	33	32	− 2	25	34	33	+1	+1	II*
7	75 F	+ 7	25	32	31	+ 6	25	34	32	+2	+1	II
8	55 M	0	25	34	32	0	25	35	33	+1	+1	II*
9	46 M	−17	25	34	30	−14	25	35	32	+1	+2	II
10	55 M	+ 4	25	34	31	− 9	25	35	31	+1	0	I*
11	75 M	− 6	24	34	32	− 8	25	35	33	+1	+1	II
12	78 M	− 8	25	35	34	+ 4	25	36	35	+1	+1	I
13	68 M	− 2	24	34	30	− 7	25	35	31	+1	+1	I
14	61 M	− 8	25	33	31	−11	24	34	32	+1	+1	II
15	63 M	− 8	25	34	31	− 6	24	35	33	+1	+2	I
16	46 M	0	25	33	31	+ 2	25	34	32	+1	+1	I
17	60 F	−11	25	34	31	− 8	25	35	33	+1	+2	I
Average	57		25.1	33.6	31.3		25.0	34.8	32.5	+1.2	+1.2	

*Surgical sympathectomy.

Table 2

Temperatures before and after Unilateral Lumbar Sympathectomy in Occlusive Arterial Disease: Group 2

Case	Age, sex,	Presympathectomy BMR	Presympathectomy Temperature, °C. Air	Presympathectomy Temperature, °C. Sural Muscle	Presympathectomy Temperature, °C. Sural Skin	Postsympathectomy BMR	Postsympathectomy Temperature, °C. Air	Postsympathectomy Temperature, °C. Sural Muscle	Postsympathectomy Temperature, °C. Sural Skin	Differences Muscle	Differences Skin	Sweating pattern
1	64 M	0	25	34	32	+ 2	25	34	32	0	0	II*
2	52 M	− 5	24	35	33	− 6	25	35	33	0	0	II*
3	66 M	−19	26	34	32	− 4	26	34	32	0	0	I*
4	71 M	−11	26	34	31	−13	26	34	31	0	0	I*
5	61 F	+31	26	34	32	+24	26	34	32	0	0	I*
6	69 M	+ 1	26	32	30	0	26	32	30	0	0	I
7	76 F	− 7	25	34	32	+12	24	34	32	0	0	I
8	30 M	0	25	35	33	− 6	25	35	33	0	0	I*
9	69 M	− 7	25	34	32	+ 5	25	34	32	0	0	I
Average	62		25.4	34.0	31.8		25.3	34.0	31.8	0	0	

*Surgical sympathectomy.

excluded, the average age of the group was 62 years. Thus, the studies were carried out on older persons.

Studies of the patients after performance of unilateral lumbar sympathectomy were divided into two groups: (1) 17 patients who had elevation of the temperature of the gastrocnemius muscle and the skin of the sural region; and (2) nine patients who had no increase in the temperature of the gastrocnemius muscle and the skin of the sural region.

The sweating patterns of all of these patients were divided into two groups: (1) anhidrosis of the entire lower extremity, from the inguinal region down, and (2) anhidrosis from the knee down. Anhidrosis of the entire extremity represents removal of the upper three lumbar ganglia, and anhidrosis of the leg from the knee down represents sympathetic denervation of the second and third lumbar sympathetic ganglia and rami.

Patients who had areas of spotty sweating

over the entire extremity or irregular hydrotic areas were excluded, since no effect of the sympathetic denervation could be anticipated.

Members of group 1 (table 1) are patients who had elevation of the temperature of the gastrocnemius muscle and of the skin of the sural region after unilateral lumbar sympathectomy. The average postoperative increase in temperature of the gastrocnemius muscle in 17 patients was 1.2 C., with a range from 1 to 2 C.* Also, the increase in the skin of the sural area averaged 1.2 C., with a range from 0 to 2 C. Figure 1 depicts the effects of lumbar ganglionectomy in a typical patient of this group. About 15 minutes was considered to be an adaptation period, and therefore the last, or most stable, temperature reading after a period of 20 minutes represents the temperature recorded in all tables. The average age of these 17 patients (excluding the 21-year-old woman and the 30-year-old man) was 61 years. Two patients had ulcers on their feet. There was a constant increase in the temperature of the muscle and sural region.

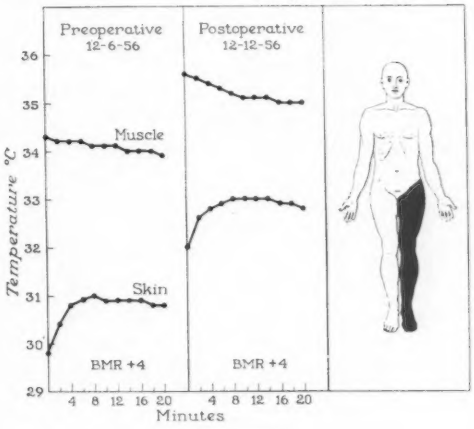

Figure 1

Data from patient in group 1. Elevation of the temperature of the gastrocnemius muscle and sural skin area after left lumbar ganglionectomy is parallel. The area of anhidrosis (dark shaded) of the left lower extremity after sympathectomy corresponds to the effects of removal of the first, second, and third lumbar sympathetic ganglia.

The Sural Muscle and Skin Temperatures

The patients in group 1 were again divided into two groups on the basis of the type of sympathetic denervation performed: (1) surgical sympathectomy, and (2) chemical sympathectomy. No significant change in the increase in the temperature of the gastrocnemius muscle and sural skin after adequate surgical sympathectomy as opposed to a similar change after adequate chemical sympathectomy could be noted.

Members of group 2 (table 2) were nine patients who had no increase of temperature in the gastrocnemius muscle and skin of the sural region after unilateral lumbar sympathetic denervation. Three patients had ischemic ulcers on the toes. Figure 2 depicts the effects of lumbar ganglionectomy in this group.

Discussion

Frequently it has been said that sympathetic denervation of the skin decreases the flow of blood through the underlying muscle. Various factors have been concerned with such observations. First, different methods

*In normal persons the gradient of temperature from the internal temperature of 37 C. is 33 to 35 C. for muscle temperature and 30 to 34 C. for skin temperature; thus the changes are not great and an increase of 1 to 2 C. indicates a significant change in temperature.

In contrast to the findings in the patients after sympathectomy, 10 patients similar to those in group 1 were given 5 mg. of nylidrin hydrochloride (arilidin) intramuscularly and intra-arterially. No change in skin or muscle temperature occurred. If sympathetic denervation of the lower extremities increased the circulation in the skin by shunting the flow of blood from the muscle to the skin, then a lowered or an unchanged temperature of the muscle should result, but instead, the temperatures of both the skin and muscle increased.

In these patients with severe arteriosclerosis, sympathectomy is carried out only to prevent impending gangrene or for the relief of pain; thus it was not possible to exercise these patients.

There remain some challenging problems to be attacked in this field, but at present the methods are not adequate for study of the circulation in man. The new electronic methods for the measurement of blood flow necessitate cutting down on an artery, an action which is not justifiable in man to determine the blood flow.

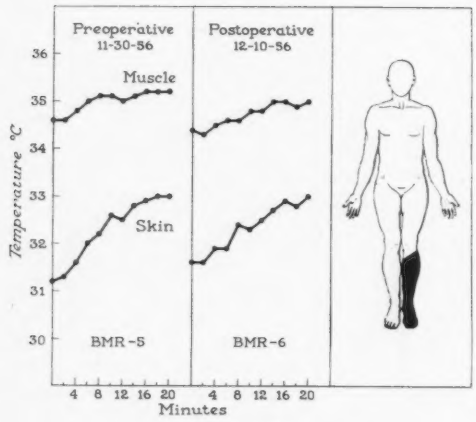

Figure 2

Data from patient in group 2. Temperatures of the gastrocnemius muscle and sural skin were not significantly influenced by left lumbar sympathectomy. The anhidrosis corresponds to the effects of second and third left lumbar sympathectomy. However, this should be adequate for the denervation of the sural skin area.

have been used to determine the flow of blood and each method has its own inherent error. Some confusion has arisen because the status of the individual has not been sufficiently controlled. We have learned that environmental temperature, position of the extremity, food, and the basal metabolic rate are important factors that exert effects on studies of the circulation. After sympathectomy a sweating test has been used to determine the completeness of the operation, particularly because of the variation in the distribution of the sympathetic nerves.

None of the patients reported upon in this series were suitable candidates for bypass arterial graft procedures because they had diffuse disease of the arteries. Likewise, lumbar sympathetic denervation could not be expected to produce marked vasodilatation; however, it would produce vasodilatation if a vasospastic component was present.

Most of the factors known to influence studies of temperature could be minimized by study of the patients under so-called basal conditions.

The symmetric difference between temperatures of the skin and in deep tissues in the extremities under normal conditions was found to be very small. Lippross[3-5] found an average temperature difference in normal persons of symmetric points of only 0.2 C. He also could demonstrate in a large series of cases that the temperature in repeated examinations within days or weeks under basal conditions in the same person, without marked progressive occlusive arterial disease, remained within the same range.

In the 26 patients who had diffuse occlusive arterial disease studied in this series, lumbar sympathectomy was thought to be the treatment of choice. The separation into two groups was based on temperatures of the skin and muscle in the sural region after performance of unilateral lumbar sympathectomy. In group 1, which consisted of 17 patients, a parallel increase in the temperature of the gastrocnemius muscle and sural skin after unilateral lumbar sympathetic denervation could be observed. This postoperative elevation of temperature, which represents an increase in the flow of blood in the measured area under basal conditions, presumably is based on the release of vasospasm superimposed upon diffuse organic disease.*

Group 2 was composed of the remaining nine patients who had what clinically was the same diffuse occlusive arterial disease; however, their condition probably was more advanced.† These patients obtained no benefit

*The exact nature of this action has not been determined in the human being.

†If measurements of the skin temperature of the lower extremities of patients with peripheral arterial disease are made before and after the oral ingestion of cobaltous chloride in a saturated solution of 90 per cent ethyl alcohol, the increase in the temperatures of the skin of the extremities, in spite of the absence of peripheral pulsations, would indicate that vasodilatation of the collateral circulation took place. On the other hand, in the absence of peripheral pulsations, if there were no increase in the skin temperatures of the lower extremities, this would indicate that the collateral circulation was not adequate and that, often, impending gangrene or even gangrene was present. Patients in group 2 had the latter condition.

from unilateral lumbar sympathectomy so far as the postoperative temperature in the gastrocnemius muscle of the sural skin is concerned. No change from preoperative values could be observed. The temperatures remained stable. Moreover, clinically no improvement was noted in comparison with the preoperative condition. No acute exacerbation of the disease was noted. It would appear that these nine patients had organic changes of the arteries without the presence of a significant vasospastic component. Thus, no effect from sympathetic denervation could be observed.

Summary

A group of 26 patients who had peripheral occlusive arterial disease of the lower extremity were studied before and after chemical or surgical unilateral lumbar sympathectomy. The temperatures of the gastrocnemius muscle and of the skin of the sural area were determined simultaneously preoperatively and postoperatively. Only patients who had undergone successful unilateral lumbar sympathetic denervation based on the postoperative area of anhidrosis were included. The data were obtained under basal conditions among the 26 patients, and the persons studied were divided into two groups. Group 1 was composed of 17 patients (65 per cent) who had a definite parallel increase of 1.2 C. in the temperature of the gastrocnemius muscle and the skin after unilateral sympathectomy. In group 2 (nine patients or 35 per cent) the temperature of the gastrocnemius muscle and the skin of the sural area was unchanged after unilateral sympathectomy. Since none of these patients were suitable for surgical bypass arterial-grafting procedures and all were in the older age group, not too much could be expected from the standpoint of an increase in temperature. However, when the temperature of the skin after operation increased, the temperature of the gastrocnemius muscle also increased.

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Consider the virtues of taciturnity. Speak only when you have something to say.—SIR WILLIAM OSLER. *Aphorisms From His Bedside Teachings and Writings.* New York, Henry Schuman, Inc., 1950, p. 85.

The Influence of Standard of Living on Blood Pressure in Fiji

By IAN MADDOCKS, M.B.

THE HURRY and worry that accompany Western civilization are often invoked as etiologic factors in hypertension. In Fiji and the Gilbert Islands some populations do not show the higher blood pressures of later life characteristic of Western populations.[1] It is tempting to associate the apparently indolent, secure, and unhurried life of the Pacific Islander with this relative freedom from hypertension.

To test the possible influence of the "Western" way of life among these Pacific populations, I set out to compare in the same race the blood pressures of a middle-aged group that had led such a life, with a group that had not. Few Fijians and hardly any Gilbertese lead "Western" lives, but there is such a group among the Indians of Fiji. The rural Indian population of Fiji has been studied and shown to have an incidence of high blood pressure almost as low as among Fijians.[2] There are numbers of Indian men in business and the professions in Fiji, whose wealth and influence are increasing. Most of them have lived in relative physical comfort compared with the rural Indians. They have been concerned with clerical work rather than manual labor, and have accepted the strains of business competition. It is a common prejudice among members of this group that they suffer from high blood pressure, because, they say, high blood pressure is associated with worry and with drinking alcohol.

During March 1960, a survey of casual arterial pressure was conducted among the Indian business men of Suva, Fiji, to compare them with the blood pressures of the previously reported rural population.

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Methods

Selection of Subjects

The sample sought comprised shopkeepers (general merchants, jewelers, tailors), transport and building contractors, and professional men (doctors, lawyers, insurance agents, teachers). To avoid a selection that might have been conditioned in any way by the health of the subjects, lists were obtained from the two Indian Clubs of all members thought to be over 40 years of age, and from the Civil List of all men over 40 years of age earning more than F£500 annually, and all head teachers. A total of 146 names was collected, and of these 121 are included in the final sample. The remaining 25 either could not be located in Suva or were seen under circumstances that did not satisfy the criteria for the standard measurement of blood pressure. The Indians of Fiji originally came from many different parts of India. The genetic background of this urban sample was mixed, but is thought to be very similar to the genetic background of the rural sample with which comparison is made.

Measurement of Blood Pressure

The technic of measuring blood pressure and arm circumference has been described in detail elsewhere.[2] Both this survey and that of the rural sample were conducted by the same observer. Subjects were visited in their offices or shops, and were kept seated for at least 10 minutes before the blood pressure was recorded.

Results

Mean systolic and diastolic pressures for this group of urban Indians are compared with those previously reported for rural Indians in table 1. Figure 1, which illustrates the comparison, shows that the means of both systolic and diastolic pressures of the urban population were consistently higher than those of the rural population. The significance of this difference was investigated by comparing the linear regressions of blood pressure

Table 1

Arterial Pressure (mm. Hg) of Rural and Urban Indian Men

	RURAL					URBAN				
		Systolic		Diastolic			Systolic		Diastolic	
Age	Number	Mean	Standard deviation	Mean	Standard deviation	Number	Mean	Standard deviation	Mean	Standard deviation
30–39	394	121.3	14.0	77.4	11.6	18	126.1	20.5	88.1	12.6
40–49	448	126.1	18.8	79.4	13.4	55	130.1	20.5	87.0	14.3
50–59	187	134.1	26.2	81.3	15.4	39	140.1	21.6	88.6	12.8
60–69	179	135.9	24.1	77.9	11.2	9	145.0	22.2	88.3	8.6

Table 2

Arterial Pressure Corrected for Arm Circumference in Rural and Urban Indian Men

	RURAL			URBAN		
Age	Arm circumference	Corrected systolic	Corrected diastolic	Arm circumference	Corrected systolic	Corrected diastolic
30–39	26.6	123.3	69.7	27.9	127.2	79.4
40–49	26.3	128.7	72.1	27.7	131.2	78.3
50–59	25.7	137.4	74.4	27.5	141.0	79.5
60–69	24.2	141.2	72.1	26.6	147.2	80.6

on age in the two populations by means of an analysis of covariance. The regressions for both systolic and diastolic pressures were significantly different in level but not in slope in the two samples.

Table 2 compares the mean arm circumferences in the two populations, and shows the effect of applying the correction for arm circumference recommended by Pickering, Roberts, and Sowry.[3] The urban Indians had greater mean arm circumferences at all ages, but the differences between the corrected means remained significant, though reduced.

Discussion

For a systematic and significant difference to occur between the blood pressures of two populations, there need not be any way in which they can be contrasted. Bøe, Humerfelt, and Wedervang[4] in their survey in the City of Bergen, found such a difference between the two halves of that apparently homogeneous city. Here, therefore, where two populations have been chosen to contrast in their way of life, the differences found in their blood pressures do not necessarily depend upon that contrast, but could occur from chance, or from the operation of other factors. The almost universal concern shown by the urban Indians about the level of their blood pressures, for example, may have been a sufficient emotional stimulus to raise their pressures above those of the rural population, who were generally less aware of the significance of blood pressure. This would have its effect more upon the systolic pressure, and the fact that the diastolic pressure is also significantly higher in the urban group probably means that the emotion is not the cause of the blood pressure difference.

A factor that might be responsible for the difference is body weight. The increase of blood pressure with body weight has been demonstrated in many races. Padmavati and Gupta[5] found that the average systolic and diastolic pressures of a group of urban Indians were higher than a poorer rural group, and noted that the urban group had higher average body weights. Body weight was not measured in both the Indian population samples in Fiji, but its influence can be assessed from the measurements of arm circumference. From data available for part of the rural Indian population it has been calculated that an increase of 1 cm. in arm circumference is associated with an average increase of 3.7 Kg.

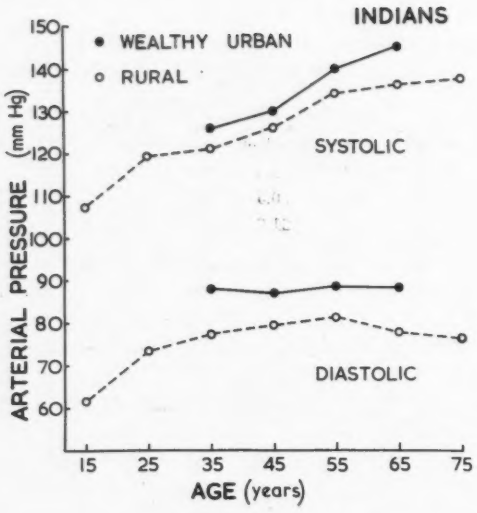

Figure 1

The relationship between mean systolic and diastolic pressures and age for wealthy urban and rural Indian men in Fiji.

in body weight. The average difference between the arm circumference of the two Indian samples (1.6 cm.) therefore represents a difference of approximately 6 Kg. in their average body weights. Bøe, Humerfelt, and Wedervang[4] estimated that an increase of 10 Kg. in body weight was associated with an increase of 3 mm. Hg in systolic pressure and 2 mm. Hg in diastolic pressure. Weight differences between the two Indian populations, on those figures, are too small to explain the differences in their average blood pressures.

Table 3 compares the prevalence of systolic pressures greater than 180 mm. Hg and diastolic pressures greater than 100 mm. Hg in Fijians,[2] Gilbertese,[1] the two Indian populations, and a London population[6] of men aged 40 to 69 years. The levels 180 and 100 mm. Hg were chosen because they are often taken in defining high blood pressure. The percentage of high pressures is least in Gilbertese, and gradually increases through Fijians, rural Indians, urban Indians, and Europeans. As the blood pressures of more racial groups are studied, it will probably become apparent that there is a continuous gradation from

Table 3

Prevalence of Hypertension in Men Aged 40 to 69 Years

Race	Systolic pressures 180 mm. Hg and over		Diastolic pressures 100 mm. Hg and over	
	Number	Percentage	Number	Percentage
Gilbertese	1	0.05	11	5.5
Fijian	15	2.8	39	7.3
Rural Indian	32	3.9	76	9.3
Urban Indian	4	3.7	25	22.6
Londoners	29	6.8	53	12.5

those populations in which essential hypertension is rare (e.g., Gilbertese) to those among whom it is a major disease and cause of death (e.g., Europeans). That two groups of Indians, apparently similar except for the Western way of life of one of them, form a step in this gradation, and that the influence of Western culture among these peoples parallels the incidence of high pressures among them, suggests that some environmental factor or factors associated with the Western culture pattern causes blood pressure to rise.

The sorting out of the possible operative influence in the Western culture pattern is a matter of great complexity. Diet, alcohol intake, exercise, and the frequency of psychologically stressful situations may all be relevant. Even if the inheritance of essential hypertension is eventually defined in terms of a single gene system, environmental factors could still have important triggering effects. The continuing study of population samples in poorer countries where hypertension is uncommon, as they adopt Western ways, may be the best available means for discovering and assessing these factors.

Summary

A group of Indian men in Suva, Fiji, selected for their relatively high standard of living had average systolic and diastolic blood pressures higher than those of the sample of the local rural Indian male population. There is gradation in the incidence of high blood pressure among several races of the Pacific Islands that parallels the degree to which they have been influenced by Western culture.

Acknowledgment

My thanks are due to Dr. Dill Russell, Director of Medical Services Fiji, for permission to undertake these studies and to officers of the Administration of Fiji and the Colonial Sugar Refinery Company for their assistance in the field work. I am grateful to Professor R. R. H. Lovell for his valuable advice and criticism.

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The first condition to be fulfilled by men of science, applying themselves to the investigation of natural phenomena, is to maintain absolute freedom of mind, based on philosophic doubt. Yet we must not be in the least sceptical; we must believe in science, i.e., in determinism; we must believe in a complete and necessary relation between things, among the phenomena proper to living beings as well as in all others; but at the same time we must be thoroughly convinced that we know this relation only in a more or less approximate way, and that the theories we hold are far from embodying changeless truths. When we propound a general theory in our sciences, we are sure only that, literally speaking, all such theories are false. They are only partial and provisional truths which are necessary to us, as steps on which we rest, so as to go on with investigation; they embody only the present state of our knowledge, and consequently they must change with the growth of science, and all the more often when sciences are less advanced in their evolution.—CLAUDE BERNARD. *An Introduction to the Study of Experimental Medicine*. New York, The MacMillan Company, 1927, p. 35.

The Identification of Right-to-Left Shunts in the Central Circulation by the Injection of Ether

By ROBERT S. FRASER, M.D., RICHARD E. ROSSALL, M.D., JOSEPH DVORKIN, M.D., AND CESAR VALLE-CAVERO, M.D.

SEVERAL METHODS are now used in conjunction with cardiac catheterization for localizing and quantitating right-to-left shunts. These include the recording of indicator-dye concentration curves after selective intracardiac dye injection,[1-4] the external recording of radioactivity following injection of radioactive materials,[5, 6] and the use of cardioangiograms or cineangiograms to picture the course taken by contrast media introduced selectively through the cardiac catheter.[7]

Such methods may provide both qualitative and quantitative information, but in some instances they embody either theoretical or practical disadvantages to the patient. These include the theoretic hazards inseparable from the use of radioactive materials, the cost of special equipment and its early obsolescence owing to improvements in design, and finally the small increase in risk associated with repeated angiocardiograms.

We believe that we are justified in reporting our results using a qualitative, simple, and safe method of identifying the origins of right-to-left shunts. This information, in addition, permits accurate selection of the best site from which to perform intracardiac injections of contrast media. While the use of indicator-dilution curves has been recommended for such preliminary localization of shunts,[8] the test to be described requires no special equipment. Although it does not lend itself to quantitative interpretation, the ether test will always give a definite positive or negative result.

Method and Material

The tests were performed as described by Donzelot et al.[9] Anesthetic ether was drawn into a 1-ml. tuberculin syringe in amounts of 0.05 ml. for infants and small children and 0.1 to 0.2 ml. for adults. During the injection, the syringe was tilted in such a way that the layer of ether was injected first, followed by saline. The injection and response times were not recorded because of the purely qualitative nature of the response.

Rapid injections of these small amounts of ether through the cardiac catheter into the pulmonary circulation normally caused the patient to cough but produced no other subjective effect. Such a response was termed "negative." In the presence of a right-to-left shunt, however, such an injection resulted in a dramatic complaint by the patient of "pins and needles" or "pricking and burning" around the mouth, nose, and forehead. When the right-to-left shunt occurred through a patent ductus arteriosus, the patient complained of similar sensations in the buttocks and feet. Such responses are termed "positive."

The application of this test to infants and children depends on the use only of sedation as opposed to general anesthesia. All of our patients in this age group were sedated as recommended by Keith, Rowe, and Vlad.[10] In infants, a positive ether test was indicated by a sharp cry, often accompanied by an abrupt grimace.

In every patient a negative test was demonstrated by injection of ether distal to the site of the right-to-left shunt. The tests were performed with the catheter tip in the right or left pulmonary artery, main pulmonary artery, outflow and inflow areas of the right ventricle, right atrium, and superior vena cava. If a test was positive at any one of these positions, no more proximal tests were made.

The results to be described were obtained from our first 562 patients in whom cardiac catheterization was carried out in the course of investigation of suspected congenital heart disease. Cyanosis, evidence for arterial desaturation revealed by ear oximetry, or systemic levels of systolic pressure in the right ventricle at catheterization were accepted as indications for ether tests. These tests were performed on 109 patients. The results reported here, with one exception, are from ether tests on 57 of these patients whose diagnoses were confirmed at operation or by necropsy. The exception is presented separately as a case report.

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Supported in part by a grant-in-aid from The Alberta Heart Foundation.

Results

The results are summarized in table 1. In 43 patients, ether tests were positive from one of the following points of injection: main pulmonary artery, right ventricle, right atrium, venae cavae, or subclavian vein. In 42 instances the site of right-to-left shunting, predicted from the ether test, was confirmed. The most common lesion in this group was tetralogy of Fallot (19 patients). Five patients had pulmonary stenosis associated with atrial septal defects and four others had transposition of the great vessels. Three patients had pulmonary hypertension with right-to-left shunts through ventricular septal defects. There were two examples of pulmonary stenosis associated with both atrial and ventricular septal defects, two with huge atrial septal defects with bidirectional shunts, and two with aorticopulmonary windows. Single examples of a variety of combined lesions were found in the remaining six patients.

Thirteen of the 43 patients under discussion had arterial oxygen saturations of 90 per cent or greater at the time of catheterization. The specificity of the test was illustrated by the demonstration of positive tests in these patients. In eight of the 13, the arterial oxygen saturation at rest was 95 per cent or more. Despite the minimal degree of right-to-left shunt in these patients the presence and site of the shunt were correctly identified.

The single instance in which the site of right-to-left shunting was wrongly interpreted from the ether test was in a patient with tetralogy of Fallot. Only one injection of ether was made into the right ventricle (from a position in mid right ventricle) and this resulted in a negative ether test. Subsequently, a positive result was obtained from an ether test in the right atrium, and the shunt was wrongly interpreted as being at atrial level. Had a test been made in the inflow region of the right ventricle, we believe that this mistake would not have occurred.

A group of 11 patients with negative results were all persons in whom high right ventricular systolic pressures indicated the possibility of small right-to-left shunt. In each instance, the negative result of the ether test was confirmed at operation or autopsy.

Table 1

Results of Ether Tests in 57 Patients

Ether test		No. of patients
Positive	a) Site confirmed at operation or autopsy	42
	b) Site proved wrong at operation	1
Negative	a) No right-to-left communication at operation or autopsy. Systemic level of right ventricular systolic pressure	11
	b) False negative in presence of proved right-to-left communication	3

False-negative results were recorded in three instances among the earlier patients in the series. Two of these patients had tetralogy of Fallot. In retrospect, it seems probable that the injection from the right ventricle was made from a position distal to the septal defect in one patient, and in this instance no test was made from the right atrium. For the second patient it seems likely that too small an injection of ether was made (0.05 ml.) in a two-year-old child who was heavily sedated. The third patient had an endocardial cushion defect with pulmonary hypertension and cyanosis. Ether tests were done from the pulmonary artery and right ventricle, and both were negative. No test was done from the right atrium and, in this instance, the right-to-left shunt may well have been at this level. Thus we think that two of the three false-negative results would not have occurred had we performed a complete series of ether tests as was the case in our later patients.

A further instance in which ether tests proved valuable is illustrated by the following report of a patient not included in the above series.

Case Report

A 36-year-old man was investigated for cyanotic congenital heart disease and was found to have severe pulmonary stenosis with an interatrial septal defect. Ether tests were performed during cardiac catheterization and proved to be negative

from the right ventricle and positive from the right atrium. In addition he also had a left superior vena cava.[11] The intracardiac defects were repaired with the use of cardiopulmonary bypass. Slight cyanosis (85 to 90 per cent) persisted, however, for a few days following surgery. Six months later he returned for further investigation, in the course of which a second cardiac catheterization was performed. Ear oximetry had been done with values of 98 per cent at rest, dropping to 93.5 per cent on exercise, suggesting a residual small right-to-left shunt. During the catheterization it was found that the right ventricular systolic pressure had fallen from a preoperative level of 130 mm. Hg to 66 mm. Hg, and ether tests from the right ventricle, right atrium, and superior vena cava were all negative. The final test was performed with the catheter tip in the left subclavian vein with a prompt positive result. The termination of the left superior vena cava had not been searched for at operation, but the results of the ether test provided strong evidence that the small residual right-to-left shunt was due to drainage of venous blood from this vessel directly into the left atrium.

Discussion

Donzelot et al.[9] described selective ether tests, which they believed provide accurate information and are simple to perform. The amounts of ether recommended were somewhat greater than those we used, but there were few complications in Donzelot's series. Minor difficulties included headache, nausea and occasional vomiting; three infants from his series of 633 cyanotic patients had convulsions and one patient had a transient hemiplegia.

We observed no ill effects whatsoever in our smaller series and would endorse the opinions held by these previous workers that the test is simple, safe, gives accurate results, and allows immediate interpretation—an important consideration when intracardiac angiograms are being planned.

Summary

A method is described for localizing central right-to-left shunts by means of anesthetic ether injected through a cardiac catheter at various sites during cardiac catheterization.

The presence and location of right-to-left shunts were correctly demonstrated in 42 of 43 patients in whom the diagnosis was later confirmed at operation or autopsy. The instance in which the site was interpreted incorrectly is explained.

Three false-negative results were obtained from the test and reasons for these are also given.

In our view the test is simple, safe, gives accurate results, allows immediate interpretation, and requires no special equipment. It has proved to be a most useful test for preliminary localization of shunts prior to selective angiocardiography.

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The Use of Ascorbate Dilution Curves in Cardiovascular Diagnosis

Applications of a Technic for Direct Intravascular Detection of Indicator

By PETER L. FROMMER, M.D., WILLIAM W. PFAFF, M.D., AND EUGENE BRAUNWALD, M.D.

AT THE PRESENT time, indicator-dilution curves are one of the most important technics employed in the investigation of the circulation. The earliest of these studies were carried out by the rapid serial collections of blood samples and their subsequent photometric analysis.[1] This ingenious but cumbersome method was replaced by the continuous withdrawal of blood in front of a photoelectric cell, thus permitting the direct inscription of time-concentration curves.[2] Although this approach has greatly facilitated application of the indicator-dilution principle, a number of drawbacks have remained. Most of them are related to the unavoidable physical separation of the intravascular sampling site and the external detector. Thus, the loss of blood may become significant, particularly when multiple dilution curves are necessary. Secondly, distortion of the curve results during transit from sampling site to the detector.[3] Finally, it may be difficult to obtain dilution curves from the central circulation, since the blood sample must traverse a long catheter. Accordingly, considerable effort has been directed toward the development of technics that permit placement of the detector directly into the blood stream.[4–7]

Clark and his associates[8–11] have recently introduced a new group of indicators, chemical reducing agents, that can be detected with intravascular platinum electrodes. This report describes the technics and instrumentation employed in this laboratory with sodium ascorbate as an indicator; particular emphasis is placed on the dilution curves obtained from an electrode incorporated into a catheter introduced into the central circulation.

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Theory and Instrumentation

Following the injection of ascorbate into the circulation, its concentration at any intravascular site may be measured by the increase in current that it produces between an intravascular platinum sensing electrode at this site and a reference electrode on the skin. The basis for this signal is the oxidation of ascorbate ion, which occurs upon its contact with a positively charged platinum surface, and the resultant release of electrons. The current produced is proportional to the ascorbate ion concentration at the electrode surface, but it is also affected by the previous physical, chemical, and electrical treatment of the electrode, its size and shape, and the voltage applied to it, as well as a number of other influences. During the inscription of an ascorbate dilution curve, however, the factors other than the concentration of the indicator remain virtually constant.

The system employed (fig. 1) consists of a bright platinum sensing electrode incorporated on a cardiac catheter (1), or (2) threaded through a modified Cournand needle (3), and connected to a control box (4). A silver reference electrode (5) is placed on the skin. The control box applies +1 volt to the platinum electrode and the current flowing between the sensing and reference electrodes develops a voltage across a series resistor, and this voltage is applied to a recorder (6). A sterilized clip lead (7) is used to protect the sterile field.

The cardiac catheter is a commercially available* Cournand catheter with a 90 per cent platinum-10 per cent rhodium electrode, 2 mm. in width, encircling the catheter several millimeters proximal to its tip. The wire to the electrode is embedded in the catheter wall, leaving the lumen patent. The arterial electrodes are prepared by melting one end of a 0.010-inch diameter platinum wire into a sphere, slightly less than 0.030 inch in diameter. Thirty-gage, thin-wall Teflon tubing is

*U. S. Catheter Co., Glen Falls, New York.

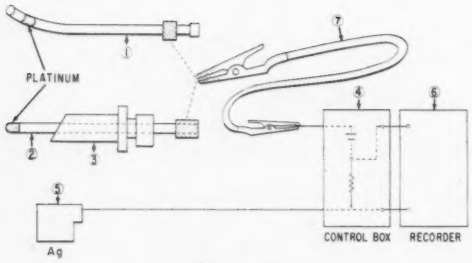


Figure 1

Schematic diagram of the instrumentation employed for the recording of ascorbate-dilution curves. Numbers are described in the text.

threaded over the wire and sealed to the electrode with Hysol cement.* A small metal contact is soldered to the other end of the platinum wire. The electrode tip is cleaned with acetone, rinsed with water, and prepared for autoclaving. The tip of the no.-18 Cournand needle is modified by blunting the bevel and removing all internal burrs (fig. 2).

Within the control box, (fig. 3), a transistor circuit maintains a 1-volt potential across the electrode terminals. The transistor also prevents the electrode current from ever exceeding 0.6 ma., thus limiting the hazard of cardiac stimulation. The electrode current is measured across one of the series resistors, R11 to R20. A resistor is selected across which not more than 10 mv. is developed by the peak current of the inscribed curve. Thus the electrode voltage always remains within 10 mv. of its original value. A much larger change, e.g., 50 mv., would often introduce significant distortion into the curves. For similar reasons, if a zero offset is desired, the controls of this box are used, rather than the centering controls of the recorder.

Because of their availability, a standard recording potentiometer† or an amplifier-galvanometer combination‡ was used. However, any system would be satisfactory that can produce a full-scale deflection for a current as small as 0.5 microampere without developing more than a 10-mv. drop across the current-measuring element.

Procedure

The electrode is cleaned with saline before it is inserted into the blood stream. Following the introduction of the electrode, the sensitivity on the control box is set so that the baseline current produces approximately one fifth of the full-scale deflection. The current flow stabilizes gradually following the application of voltage to the electrode. It is often convenient to shorten this period of stabilization by first applying an excessive voltage (approximately 1.34 volts) for about 30 seconds before dropping to the 1.0 voltage. If the baseline is still falling, it may be necessary to reapply the overvoltage briefly, or if it is rising excessively, a brief period of short circuiting the electrodes (0 volts) is helpful. It is desirable to avoid frequent interruptions of the voltage applied to the electrode.

The indicator, buffered sodium ascorbate,* is injected at concentrations of 50 or 100 mg. per ml., in doses ranging between 25 mg. and 300 mg., depending on the size of the patient, the hemodynamic state, the volume of blood between the site of injection and sampling, and the intrinsic sensitivity of the electrode.

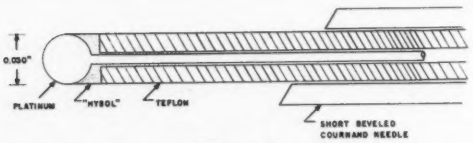


Figure 2

Schematic diagram of the platinum electrode, the Teflon covering, and the short-beveled Cournand needle.

Results

The linearity of the electrode current with the ascorbate concentration in the blood stream was examined in dogs in which various doses of sodium ascorbate were injected intravenously. The peak amplitudes, as well as the areas beneath the arterial dilution curves were found to be linearly related to the doses (fig. 4).

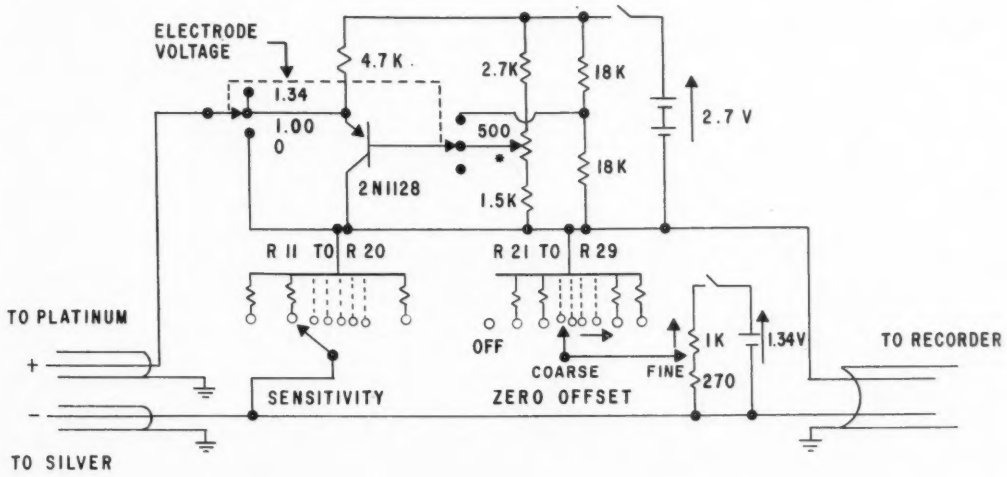
Sodium ascorbate dilution curves have been recorded in 25 dogs and in a total of 90 patients. There have been no febrile reactions or other detectable toxicity. In more than one half of the patients studied, the sodium ascorbate curves were compared with indocyanine-green dye-dilution curves, with identical injection and sampling sites; the dye-dilution curves were recorded immediately

*Available from Fisher Scientific Co., Chicago, Illinois.

†Model MR recorder, E. H. Sargent and Co., Chicago, Illinois.

‡Model 301 D. C. amplifier and rectilinear recorder, Texas Instrument Co., Houston, Texas.

*Supplied as "Ascorbic Acid" by Lederle Laboratories, Pearl River, New York.



ALL SWITCHES ARE SHORTING CONTACT TYPE.
ALL MERCURY BATTERIES.
R 21 TO R29 ∞ , 10 M, 3.3 M, 1 M, 330K, 100K, 33K, 10K, 3.3K - 10%.
FOR 10 MV RECORDER R11 TO R20: 50, 100, 200, 500, 1K, 2K, 5K, 10K, 20K, ∞
1% PRECISION RESISTORS. (DEPOSITED CARBON).
* SET FOR 1.00 V OUTPUT

Figure 3

Circuit diagram of control box.

before or after the ascorbate curves. For the paired curves, the initial portions, representing the passage of indicator through the central circulation and through any shunt in either direction, were essentially identical. It is this portion of the curve that is of diagnostic significance. In the later portions of the ascorbate curves, generated by indicator that had passed through the peripheral capillary bed and had recirculated, the peaks were smaller than the corresponding peaks in the dye curves.

Comparing the quality of the tracings on systems of equal frequency response, there were generally less artifacts coincident with the pulse in the ascorbate than in the dye curves. With the platinum electrode advanced into the thoracic vessels, these artifacts were more apparent and a signal coincident with respiration was often present, especially in tracings from the right atrium. Intracardiac electrocardiograms were present in high-frequency recordings. Occasional artifacts were noted coincident with movements of the patient. In some instances, the curves had to be repeated in order to distinguish a very small shunt from a respiratory artifact; otherwise these artifacts created no problems.

Ascorbate dilution curves sampled in a peripheral artery following injection into the right atrium of a patient without any cardiac shunt or valvular regurgitation are reproduced in figure 5. In a patient with the tetralogy of Fallot, the presence of a right-to-left cardiac shunt is evidenced by the characteristic early peak in the curves reproduced in figure 6, which were obtained following injection into the right ventricle and sampling from a systemic artery. Figure 7 is an arterial dilution curve obtained following injection into a pulmonary vein of a patient with a left-to-right shunt through an atrial septal defect. There is a sudden inter-

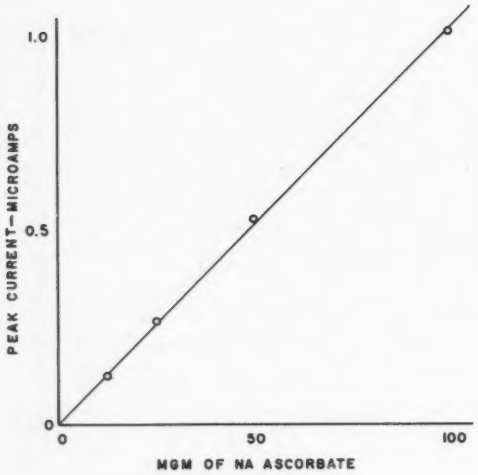


Figure 4

Relationship between peak signal and dose of sodium ascorbate injected.

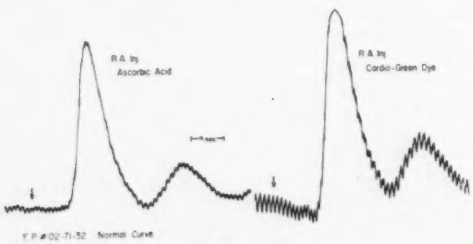


Figure 5

Ascorbate (left) *and indocyanine green dye* (right) *dilution curves recorded in rapid succession from a systemic artery in a patient without a circulatory shunt following injection of the indicators into the right atrium at the time indicated by the vertical arrows.*

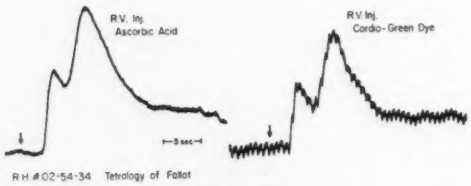


Figure 6

Ascorbate (left) *and indocyanine green dye* (right) dilution curves recorded from a systemic artery in a patient with the tetralogy of Fallot.

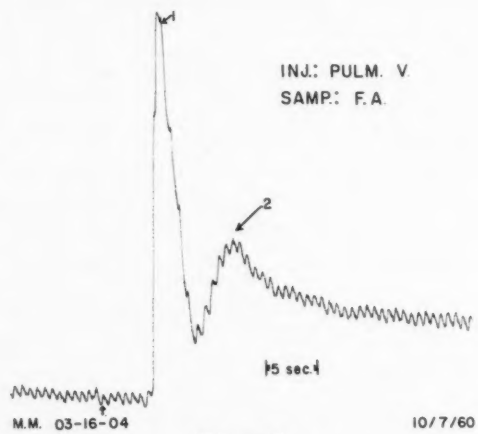


Figure 7

Ascorbate dilution curve obtained in a patient with an atrial septal defect following injection into a pulmonary vein (pulm. V.) and sampling from the femoral artery (F.A.). The first peak (1) represents the indicator that followed the normal circulatory path, while the second peak (2) represents the indicator that was shunted through the defect.

ruption of the descending limb, followed by the abnormally early recirculation curve, a pattern characteristic of arterial dilution curves following injections into the left side of the heart proximal to the origin of such a shunt.[12]

A series of intracardiac ascorbate dilution curves obtained in a patient with a large ventricular septal defect are reproduced in figure 8. In each instance the sensing electrode was near the tip of the catheter through which the injections were made. Each curve is characterized by a large, sharp, initial deflection resulting from the reaction of the electrode to the injection of ascorbate. In the curves obtained from the pulmonary artery and the right ventricle, a second peak is apparent; this is due to the early recirculation of indicator through the shunt, and it occurs only in areas at or distal to the site of entry of the shunt into the right side of the heart. In contrast, in the right atrium, a chamber proximal to the site of entry of the shunt, no second peak is exhibited. These curves may be compared to those reproduced in fig-

ure 9, which were obtained from a patient with an atrial septal defect, in whom the abnormal shunt curve (peak 2) is present both in the curve from the right ventricle and in the curve from the right atrium, thus localizing the entry of the shunt to a point upstream to the tricuspid valve. A distinct systemic recirculation curve (peak 3) is also present.

A series of intracardiac dilution curves following peripheral vein injection in the patient with the ventricular septal defect are reproduced in figure 10. The site of entry of the left-to-right shunt into the right ventricle is localized by the technic previously described.[13] The curves from the pulmonary artery and right ventricle exhibit a distinct interruption of the descending limb, signifying the recirculation of shunted indicator; this is not present in the curve from the right atrium, although the small degree of accompanying tricuspid regurgitation may have been responsible for the slight distortion of the descending limb of the dilution curve obtained from this chamber.

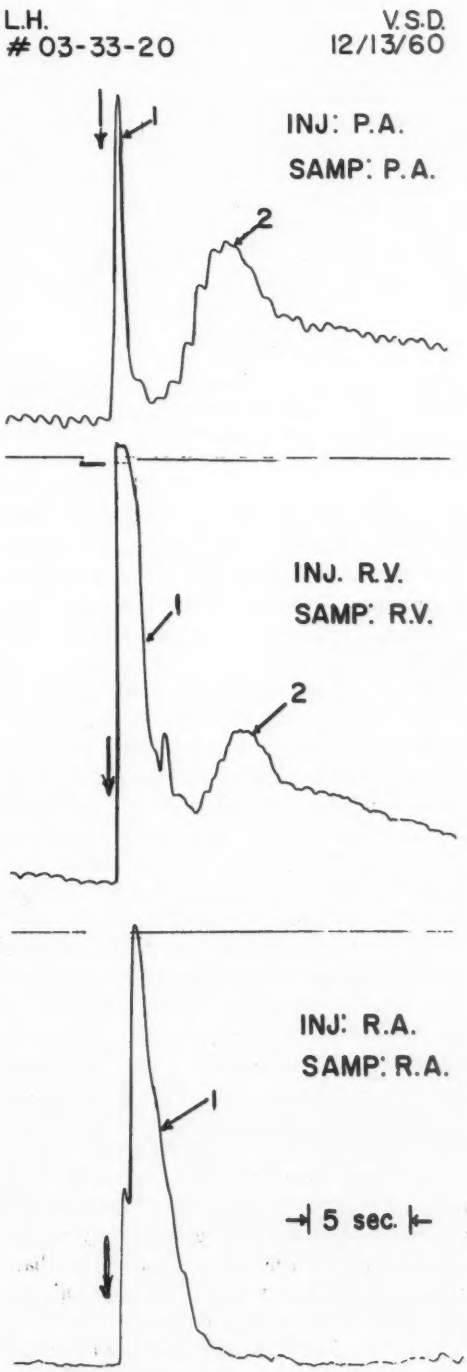


Figure 8

Intracardiac ascorbate dilution curves obtained from a patient with a large ventricular septal defect with injection into and sampling from the pulmonary artery (P.A., top*), right ventricle (R.V.,* center*) and right atrium (R.A.,* bottom*). The vertical arrows represent the onset of injection. The initial deflections (1) represent the injection of ascorbate, and the second deflections (2) represent the ascorbate that recirculated through the shunt.*

Discussion

Hydrogen, sodium ascorbate, and a number of other substances may be employed as indicators when platinum electrodes are used for direct intravascular detection.[9] The use of hydrogen was not extensively investigated in this laboratory, since the inert foreign gases (N_2O or Kr^{85}), which are not associated with an explosive hazard, permit not only the detection and localization of small left-to-right shunts,[14] as does inhaled hydrogen, but also allow determination of the magnitude of the shunt.[15] Similarly, although hydrogen dis-

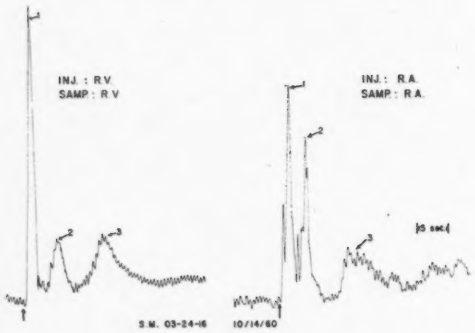


Figure 9

Intracardiac ascorbate dilution curves obtained from a patient with an atrial septal defect. Injection into and sampling from the right ventricle (R.V., left*) and right atrium (R.A.,* right*).*

solved in saline may be injected into the right side of the heart for the detection of right-to-left shunts,[10] earlier observations utilizing solutions of Kr^{85} in a similar manner indicated the practicality of quantifying such shunts.[14, 16]

It would appear likely that ascorbate equilibrates rapidly with the interstitial fluid and that a significant fraction escapes from the vascular bed during its passage through the systemic capillaries, but that only negligible amounts leave the pulmonary capillaries. Although little clinical significance should be attributed to the amplitude of the peripheral recirculation peaks of the ascorbate curves, the apparently negligible loss of this indicator from the pulmonary circulation suggests that the shunt-to-pulmonary flow ratio may be computed.

As indicated in figure 4, when the current flowing between the electrodes is measured (rather than the potential developed), a linear relationship exists between ascorbate concentration and deflection. Work currently in progress suggests that in spite of the fact that gradual alterations in the sensitivity of the electrode take place, calibration of ascorbate dilution curves is possible, thus permitting quantification of cardiac output.

In the clinical applications of the ascorbate technic in this laboratory, the recording of

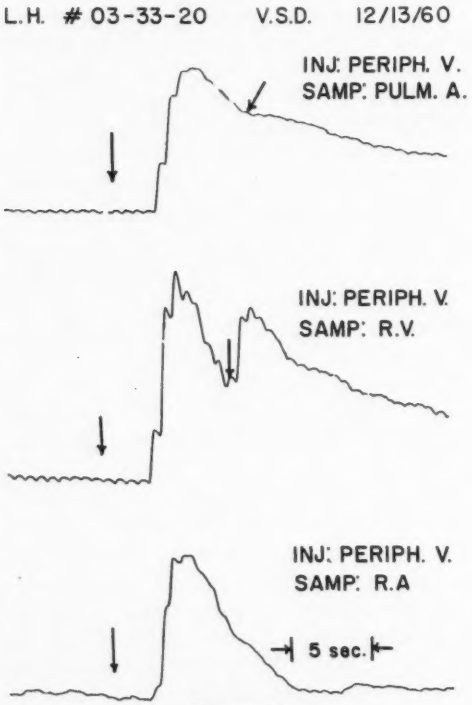


Figure 10

Intracardiac ascorbate dilution curves obtained from a patient with a ventricular septal defect. All injections were made into a peripheral vein with sampling from the pulmonary artery (top), *right ventricle* (center), *and right atrium* (bottom). *The initial vertical arrows indicate the time of injection; the second arrows indicate the abnormally recirculating indicator.*

curves from a catheter inserted directly into the heart or great vessels has been found particularly valuable. The applications have been facilitated by the availability of electrode catheters that permit both the injection and sampling of indicator through a single catheter. Although the injection of dye into the pulmonary artery and sampling of its concentration through a second catheter in the right side of the heart[17] has proved to be a sensitive technic for the detection and localization of left-to-right shunts, the use of two catheters has, in this laboratory, proved technically cumbersome. The single catheter technic described herein provides a convenient method

for simultaneously introducing both the indicator and the sampling element into the central circulation, thus permitting detection and localization of left-to-right shunts. When the sensing electrode is placed several centimeters behind the tip, the ascorbate technic may also be employed in the study of valvular regurgitation. The indicator is injected distal to the valve under study, and its concentration is detected in the chamber proximal to it.[18] Furthermore, the ascorbate technic has also been found useful in the study of patients with aortic regurgitation and those who have left-to-right shunts originating from the aorta. In these applications the electrode is introduced into the right brachial artery or the central aorta, and ascorbate is injected by means of a second catheter into the aorta at a more distal site, as described previously.[19, 20]

A distinct advantage of the ascorbate-dilution technic is the ease with which curves may be repeated. As many as 23 dilution curves have been carried out in the course of a single catheterization; the injection of up to 6.5 Gm. of sodium ascorbate has resulted in no detectable side effects. The cost of this indicator is considerably less than indocyanine-green dye. Finally, the ability to record dilution curves without the need for complex detecting devices (densitometer, oximeters, scintillation crystals) should prove advantageous in many laboratories and under many experimental and clinical circumstances.

Summary

The instrumentation and clinical applications, in this laboratory, of Clark's sodium ascorbate dilution technic are described. With this method the sensing device, a platinum electrode, is introduced directly into the blood stream, and a reducing agent, sodium ascorbate, is used as the indicator. Time-concentration curves may be obtained without the withdrawal of blood. Observations in 90 patients have indicated that the contours of the dilution curves are essentially identical to indocyanine-green dye-dilution curves, except for diminished peripheral recirculation peaks. The ascorbate-dilution technic has been found of particular value when the sensing electrode is incorporated into a cardiac catheter. This method permits injection and sampling of the indicator from the central circulation and greatly facilitates the study of circulatory shunts and of valvular regurgitation.

Acknowledgment

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The basis of the practice of medicine will always be the study of disease at the bedside by every available method, and since Sydenham is the archtype of those who believe that the most successful way of studying disease is at the bedside, his name will forever endure.

The epitaph on his monument in St. James' Church, Westminster, is magnificent and true:

"Medicus in omne aevum nobilis." A physician in any age—noble.—David Riesman, M.D. *Thomas Sydenham, Clinician.* New York, Paul B. Hoeber, Inc., 1926, p. 46.

Spontaneously Disappearing Murmur of Patent Ductus Arteriosus

A Case Report

By T. R. KEITH, M.D., AND J. SAGARMINAGA, M.D.

IN 1903, Wagener[1] reported two cases of patent ductus arteriosus with a perforated valve in the lumen of the ductus. Taussig[2] has seen two cases of patent ductus arteriosus with such a valve inside the lumen of the ductus. The disappearance of a murmur in patients who previously had an audible bruit has been mentioned by Levine and Harvey[3] and is known also to occur in a number of conditions.[4-11] Levine and Harvey in their book on auscultation, stated, "In some cases, the continuous murmur is intermittent and its presence or disappearance suggests fluctuation of the level of pulmonary hypertension," but they do not give any additional information about their experience with this type of case. Shapiro et al.[12] recently reported a case of intermittent disappearance of a murmur of patent ductus arteriosus, and they explained its disappearance by mediastinal shifting. Their patient had normal pressures in the pulmonary circuit so that, obviously, changes in the pressure gradient across the ductus could not explain the unusual auscultatory findings.

We present a case of a girl with a murmur of patent ductus arteriosus, discovered at age 10, with no evidence of pulmonary hypertension and in whom the murmur disappeared intermittently for no apparent reason. At surgery, the ductus was seen to contain a valve proximal to the pulmonary artery end, and this valve was thought to be responsible for the unusual auscultatory findings of this case.

From the Department of Cardiology, Passaic General Hospital, Passaic, New Jersey.

Case Report

S.Z., a 10-year-old white girl had a normal birth and development. Growth was somewhat slow but she was thoroughly normal otherwise. Incidence of respiratory infections was not high. Six months prior to admission, a heart murmur was discovered in the course of a routine physical examination. The patient was completely asymptomatic both before and after the detection of the murmur.

On physical examination, the patient was found to be somewhat underdeveloped. The positive findings were limited to the thorax. The heart rate was 100 and regular. The apical impulse was located at the fifth interspace in the midclavicular line. The mitral first sound was loud, and the aortic second sound was normal. At the pulmonic area, a continuous, machinery type of murmur, grade III to IV, was heard that obliterated the second heart sound. Both the systolic and the diastolic components of the murmur were well transmitted to the left side of the neck and with diminishing intensity to the right side; it was also transmitted to the apex. The phonocardiogram was typical of the condition[13] (fig. 1). The blood pressure was 110/60 mm. Hg in the right arm and 114/54 in the left arm. Femoral and pedal pulses were palpable.

Roentgenograms demonstrated one- to two-plus prominence of the pulmonary conus segment, with slight elongation of the left border on the posteroanterior view of the chest. The electrocardiogram was interpreted as showing "a horizontal position, and suggestive of left ventricular preponderance *without evidence of hypertrophy or strain,*" (fig. 2). Right heart catheterization was recommended but was refused.

The patient was admitted to the Passaic General Hospital for operation. Examination on admission, however, to the amazement of all, revealed no murmur! Several observers were present, one of whom had examined the patient when the murmur was audible. The patient was exercised, placed in various positions, made to cough,

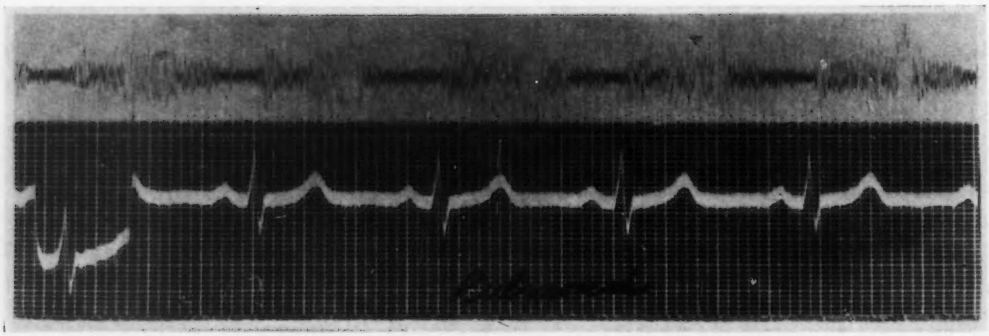

Figure 1

Phonocardiographic record showing typical murmur of patent ductus arteriosus at the pulmonic area.

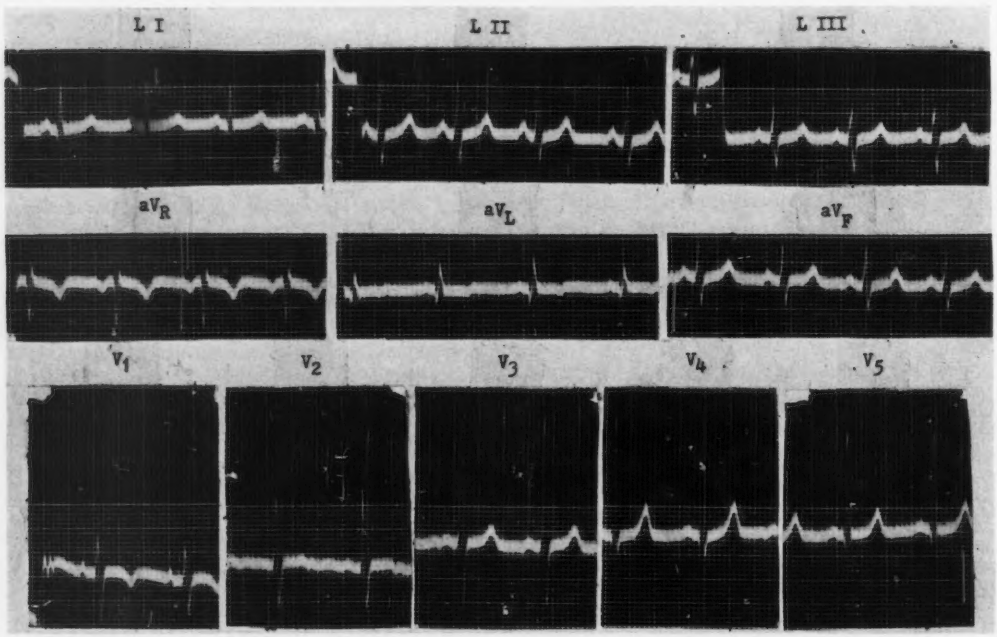

Figure 2

Electrocardiogram showing horizontal position without evidence of hypertrophy of either chamber.

and to perform a Valsalva maneuver, but no murmur was audible. She was immediately sent in a wheelchair for a phonocardiogram, but by the time she arrived in the cardiac station, the murmur was audible again!

At this point, we tried all conceivable maneuvers to make the murmur disappear, but these also were unsuccessful. The patient was carefully observed but nothing happened until the next morning when the murmur again disappeared. Again we were unable to document with a phonocardiographic tracing the disappearance of the murmur, for it was very audible after 5 minutes of silence.

Permission for right heart catheterization was again refused, and the referring physician insisted on going ahead with the operation.

On April 17, 1957, the patient was operated upon by Dr. Maxwell Chamberlain. A patent ductus arteriosus, 2 cm. in length and 1 cm. in diameter, which extended from the aorta to the bifurcation of the pulmonary artery, was found just below the subclavian artery. After the ductus was divided, it was seen to contain a valve, or veil-like structure, at the pulmonary artery end of the ductus. It was thought that this valve could account for the unusual auscultatory features of the patient, for it was easy to occlude the whole ductal lumen with the valve.

Discussion

In an extensive review of the literature we have been unsuccessful in finding a report of a similar case. The murmurs of patent ductus arteriosus are usually typical but the small percentage that are atypical usually occur in infants and children[14, 15] and are thought due to pulmonary hypertension,[4, 5, 15] low systemic pressure,[4, 9] very small diameter of ductus,[4, 9, 14] spontaneous closure of ductus,[8, 9] and shifting of mediastinal structure with occlusion of ductus.[12] Clinically, our findings were similar to those of shifting mediastinum[12] but the operative findings were entirely different. We consider it worthwhile to bring to the attention of the medical profession a case in which a murmur, loud and typical of a clinical condition (patent ductus arteriosus), became suddenly inaudible. In our patient the murmur was first heard at the age of 10 years and by the same pediatrician who had seen her after birth and who had taken care of her in all her minor illnesses of childhood. One may theorize that the ductus was closed by the valve found at surgery until the age of 10, at which time the valve split open. Only after the patient had been operated upon and the unusual pathologic structure of the ductus was known were we able to offer a satisfactory explanation for the auscultatory findings.

We have reason to believe that the pressures in the pulmonary circuit were intermittently elevated in this case, which might explain closure of the valve. There was no evidence of pulmonary hypertension in the auscultatory, roentgenologic, or electrocardiographic findings.

This, no doubt, was a case of ductus arteriosus with a left-to-right shunt exclusively, and this shunt at times completely disappeared, probably as a result of the sudden closure of the ductus by the valve. Unfortunately, no catheterization was possible in this patient. It was thought, however, that the case presented enough clinical interest to warrant a report of our findings. It is true that Taussig[2] wrote about two patients with patent ductus arteriosus in which a valve was present at the pulmonary artery side of the ductus, and in this respect our case is similar to hers. The spontaneous disappearance and later reappearance of an otherwise typical, loud murmur is in itself interesting. In this case the murmur, a so-called machinery murmur, was typical of patent ductus arteriosus; so were the other findings. In the two cases of Taussig, we are not told whether these patients had any unusual auscultatory features, although it is speculated there that certain cases of sudden appearance of a typical murmur of patent ductus arteriosus could be due to similar pathology.

Summary

A 10-year-old girl with patent ductus arteriosus had most unusual auscultatory changes, but the typical roentgenologic and electrocardiographic findings. There was an intermittent, spontaneous disappearance and reappearance of the entire machinery murmur. At surgery, a valve, or veil-like structure, was found inside the ductus at its entrance into the pulmonary artery. This valve apparently accounted for the "spontaneous" intermittent disappearance of the murmur, which was first discovered when the child was 10 years old.

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The physician without physiology and chemistry practices a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which.—SIR WILLIAM OSLER. *Aphorisms From His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 49.

CLINICAL PROGRESS

Research in Russia on Vitamins and Atherosclerosis

By ERNST SIMONSON, M.D., AND ANCEL KEYS, PH.D.

THE EFFECTS of vitamins on atherogenesis and its clinical complications have been investigated extensively in Russia during the past 15 years. The importance of certain vitamins in the treatment of coronary heart disease and other manifestations of severe atherosclerosis seems to be generally accepted. Since some of these views are not held in the United States and other Western countries, it is of interest to present here a review of the pertinent Russian literature. The references cited are representative rather than complete, but we have attempted to include the most important studies. No attempt is made here to cover the corresponding Western literature.

Research Approaches and Methods in Russia

Several approaches have been used by Russian investigators and a general comment on their validity and limitations may be useful before reviewing specific results. The Russian work is concerned with pharmacologic dosages of vitamins, usually far in excess of normal average vitamin intakes and requirements for nutritional purposes, and not with vitamin deficiencies or variations in ordinary diets. This explains, perhaps, the absence of epidemiologic studies, such as have been done elsewhere in connection with the diet.[1-4]

The evidence presented for the effects of the vitamins comes from two general sources—experiments on laboratory animals, largely confined to rabbits, and observations on the clinical course of patients with coronary heart disease treated with vitamins.

The clinical studies on this subject in Russia are subject to serious limitations. Spontaneous variability in clinical status and in the severity and frequency of symptoms is notorious in patients with coronary heart disease. The use of these criteria, particularly subjective reports of angina pectoris, is difficult and hazardous under the best of circumstances. The double-blind experiment, with a placebo control, which we now consider to be essential in the evaluation of drug therapy where subjective criteria are involved, does not seem to have been used in any of the Russian studies.

It is not even clear that other treatment, including dietary management, was discontinued or kept absolutely constant during the trials with vitamins but it does appear that the patients knew when they were being given vitamin therapy. Since a large proportion of patients with coronary heart disease report benefit from any treatment, including placebos, it is not surprising than many clinical reports of favorable action of the vitamins are found in the literature.

Finally, in the clinical studies on vitamins, as in most medical research in Russia, inadequate attention is given to the requirements for statistical analysis, as was noted previously.[5, 6] This is true of the reports concerned with objective criteria as well as those in which only subjective criteria were involved. Though the details required for statistical analysis are generally absent, it is obvious that almost all of the clinical samples were far too small to yield significance of the

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reported subjective improvement unless really spectacular benefit resulted from the vitamin therapy.

Electrocardiographic evidence of effects of vitamin therapy is claimed in some papers but there is no basis whatever to judge acceptability or significance of the evidence. Qualitative observations on some of the patients but no measurements of electrocardiographic items are reported. In a minority of the reports crude frequency distributions of qualitative electrocardiographic characteristics are given with no attempt at statistical evaluation.

The most acceptable evidence of vitamin effects in the Russian investigations on patients is provided by measurements of cholesterol and other lipids in the blood. While a decrease in cholesterol concentration in the blood does not necessarily mean clinical benefit, in general it will be agreed that this would be a desirable change and this criterion has been much used in Russia. Most Russian workers have used the Engelhardt-Smirnova method* for the estimation of cholesterol in studies both on animals and on patients. We have been unable to obtain detailed data on the reliability and validity of this method but it seems to give values in the range, though perhaps somewhat lower, that we would expect. These questions are not serious, however, when the same method is applied to the same patients in therapeutic trials.

Many of the Russian papers report data on plasma or serum "lecithin." It appears that this item is measured as lipid-soluble phosphorus and that "lecithin" is simply phospholipid. This measurement is widely considered to be significant, and emphasis is given frequently to the cholesterol/lecithin ratio though no statistically valid evidence is presented that the phospholipid value adds significantly to the information given by the cholesterol measurement.

Anitchkov's studies on the experimental production of atherosclerosis in rabbits span half a century[7-12] and the sense of priority in this field is strong in Russia. During all this time Anitchkov has insisted, and his opinion is generally accepted in Russia, that these experimental lesions are true replicas of atherosclerosis in man. The statement is made[10] that the atherosclerosis produced in rabbits is not only similar but substantially identical with that seen in man, especially when small levels of cholesterol are fed so that the development of the lesion is slow.[7] It should be noted, however, that most of the Russian studies have used large dosages and short periods (3 to 4 months). Recently, atherosclerosis has been produced in dogs by cholesterol feeding plus thiouracil in Russia, and this too is considered to be comparable to the human lesion.[13, 14]

The rabbit is generally preferred to chickens and dogs as the experimental animal.[15] Almost all animal experiments with vitamins have involved rabbits fed large doses of cholesterol so as to produce a tremendous degree of hypercholesteremia and marked lesions in the arteries within 3 to 4 months. The experiments on animals have been rigidly controlled as a rule.

Besides measurement of cholesterol and "lecithin," a major criterion of vitamin effects on atherosclerosis in the experimental animal has been visual inspection of the aorta, sometimes after staining with Sudan red. Anitchkov[11] considered this to be only a crude criterion, useful to detect gross differences, and preferred measurement of the lipid extracted from the aorta. In the absence of convenient and accurate methods, however, the Russian studies with vitamins have not utilized such measurements.

It is well known from autopsy studies on man that there is only a low degree of correlation between the severity of atherosclerosis in the aorta and that in the coronary arteries. Nevertheless, in the experimental studies in Russia with the vitamins the pathologic examinations have largely been confined to the aorta. Recently, Miasnikov[16, 17] reported atherosclerosis in the coronary arteries as well as in the aortas of 22 rabbits that had been fed cholesterol for several months. Infarction did

*Described in Predtechenko, V. M. Borovskaia and L. T. Margolina. Rukovoolstropo Laboratornim Metodam Isslodovania. Moskba, 1950.

not occur with the cholesterol feeding alone but the addition of thrombin injections, pituitrin, or extreme exercise produced areas of necrosis in the myocardium of some rabbits. The influence of simultaneous vitamin treatment in these situations has not been reported.

Fedoseev[13, 14] reported spontaneous electrocardiographic changes in dogs treated with thiouracil and fed massive doses of cholesterol. Atherosclerosis both in the aorta and in the coronary arteries, but not infarction, was observed in dogs treated in this way.[15]

As mentioned above, statistical tests of significance were not made in the Russian studies on atherosclerosis. We have supplied these for all their studies where sufficient data were reported.

Vitamin C

The relationship of this vitamin, as well as vitamin A, to the problem of atherosclerosis probably was studied first by I. A. Miasnikova,[18] who used rabbits fed massive doses of cholesterol. Her original publication is not accessible to us but the essential results were reproduced by A. L. Miasnikov in 1954.[19] The conclusion was that vitamin A accentuates and vitamin C inhibits the atherosclerosis produced by cholesterol feeding. In another early paper (1952) it was reported that treatment with ascorbic acid delays the serum cholesterol rise in rabbits fed cholesterol.[20]

These findings were quickly applied to clinical trials. In 1952 Tiapina[21] intravenously administered 500 mg. of ascorbic acid daily for several weeks to patients with coronary heart disease and reported a substantial decrease in the serum cholesterol concentration, as much as 150 mg. per 100 ml. in one patient. Later (1954) A. L. Miasnikov[22] reported that ascorbic acid lowered the hypercholesteremia of cholesterol-fed rabbits. The data are inadequate to judge whether the difference was statistically significant. Loviagina's and Sinitsina's data[23] show a high degree of variability in the serum cholesterol levels of rabbits treated with cholesterol for 105 days.

The treatment of patients with coronary heart disease by intravenous solution of ascorbic acid gained popularity quickly and in 1956 Sedov[24, 25] reported the results with 106 patients. They received 500 to 1,000 mg. daily for 20 to 30 days, and the treatment was repeated after an interval of 1 to 3 months. Before the treatment 23 per cent of the patients were stated to have had serum cholesterol values over 250 mg. per 100 ml., but after the treatment only 2.3 per cent had values that high. We find the reported cholesterol change is highly significant ($p < 0.0001$ by chi-square). The cholesterol level was unaffected in the patients who initially had low values, a finding in harmony with I. A. Miasnikova's work in 1947.[18] Sedov reported clinical improvement but gave no specific data.

According to Sedov,[25] the serum cholesterol level falls during the first days of treatment with ascorbic acid and is kept at a depressed level with chronic medication.

A very rapid response to intravenous ascorbic acid, with a fall in the serum cholesterol within a few hours, was reported by Tiapina,[26] but this was not confirmed by Grabenko.[27] Both Grabenko and Tiapina agreed with the other Russian workers, however, that treatment continued for several weeks or months lowers the blood cholesterol. The results obtained by Fedorova (quoted by Miasnikov[28]) were less uniform, with only 60 per cent of the patients showing a fall, 30 per cent no change, and 10 per cent an increase. According to Miasnikov,[28] a decrease in the blood cholesterol is obtained only with prolonged administration of ascorbic acid, and even then complete correction of hypercholesteremia may not be possible. Miasnikov[28] reported Tiapina's findings of an increase in the fecal cholesterol excretion in parallel with the decrease in the blood, but the details of chemical analysis were not given and no judgment is possible of what was actually measured in the feces.

Lobova[29] found that daily intravenous administration of 1,000 mg. of ascorbic acid for 10 days produced a decrease in the beta and an increase in the alpha lipoproteins in 18 among 35 patients. The responders were stated to be in an early phase of the disease, while

the 17 refractory patients were described as being in a more advanced phase.

There are some discrepancies in the reports of clinical benefits. Various studies report subjective improvement in feeling and work capacity with no specific data on controls. Lobova[29] reported that ascorbic acid improved the work capacity without change in the severity or frequency of angina. Fedorova (reported by Miasnikov[28]) found fewer anginal attacks in patients on ascorbic acid therapy.

Ascorbic acid is recommended as an auxiliary in the treatment of patients with coronary artery disease by such leading Russian cardiologists as Miasnikov,[22, 28, 30, 31] Il'inskii,[32] and Ryss.[33] The daily dosage advised is 500 to 1,000 mg. orally or 300 to 500 mg. intravenously (in glucose or physiologic saline solution). With the intravenous therapy the recommendation is a series of 20 to 30 daily injections to be repeated at intervals of 2 to 3 months. A favorable feature is stated to be that in the doses used ascorbic acid does not affect blood coagulation.[28, 34, 35]

Miasnikov,[28] writing in 1960, with the authority of a Member of the Academy of Medical Sciences and Director of the Institute of Experimental Therapeutics in Moscow, states, "Presently, ascorbic acid is widely used for prevention and therapy of atherosclerosis." He suggests also, without providing any data, that the great longevity of people in the mountain region of the Caucasus may be related to the high ascorbic acid content of their diet. Further, he states that the inhibiting effect of ascorbic acid on atherogenesis can be increased by combination with vitamin P, but the dosage and data are not provided.

If ascorbic acid inhibits hypercholesteremia and atherosclerosis, it might be expected that these conditions would be promoted by a deficiency of vitamin C in the diet. This was reported by Willis[36] to be the case in guinea pigs, and Tolmachev,[37] whose paper is not available to us, stated that scorbutic patients have an elevated level of cholesterol in the blood. Studies on this aspect have been little cultivated in Russia and the information is scanty. In the Western literature atherosclerosis has not been reported to be a prominent feature in persons suffering from vitamin C deficiency.[38-40]

When one of us (A. K.) returned from Russia in 1956 with the information about the enthusiasm there about ascorbic acid, fully controlled experiments were initiated with patients at a Minnesota State Hospital on rigidly fixed diets with and without the addition of 1,000 mg. of ascorbic acid daily in alternating periods of 3 to 4 weeks at a time.[41] Though the first trial suggested the possibility of a slight effect on the serum cholesterol concentration, more careful analysis and repetitions with various base diets failed to show any indication of a statistically significant effect, at average cholesterol levels between 160 and 200 mg. per cent, dependent on the fats in the diet. This does not necessarily contradict Sedov's results,[25] who found a decrease of cholesterol only at initial levels over 200 mg. per cent. This treatment has not, as far as we know, been applied in the Western World to patients with coronary heart disease.

Vitamin A

In I. A. Miasnikova's early experiments with vitamin A it was reported that atherogenesis in rabbits fed cholesterol is promoted by the administration of vitamin A. In the early fifties restriction of vitamin A in the diet was recommended on this account,[19] but later studies did not give consistent results, and in his latest (1960) review of the subject Miasnikov[28] states that vitamin A may be disregarded in regard to prevention or treatment of patients with atherosclerosis. Ryss[33] holds that there is a complex relationship between vitamin A and cholesterol metabolism. It is suggested that hypercholesteremia may be produced by vitamin A administration as a result of eliminating of cholesterol from the brain and liver.

Vitamin D_2

It appears that the effect of vitamin D_2, or calciferol, on atherogenesis is generally agreed in Russia to be unfavorable. Rabbits receiving 200 mg. of cholesterol in the daily diet for 90 days showed increases of 200 to

300 per cent in the serum cholesterol level and grade 2 to grade 3 atherosclerosis in the aortas. The addition of 100,000 units of vitamin D_2 (0.25 mg. of crystalline calciferol) to the daily diet produced an average increase of 700 per cent in the serum cholesterol and most of the rabbits exhibited grade 4 atherosclerosis in the aorta (Bavina[42]). We have been unable to find more recent reports in the Russian literature, but restriction of vitamin D is generally recommended to patients with coronary heart disease.[28, 32]

Thiamine

According to Miasnikov[28] a large series of studies in the Institute of Experimental Therapeutics in Moscow on cholesterol-fed rabbits and on patients with coronary heart disease revealed no effects of thiamine administration. In peripheral arteriosclerosis, however, Gordon[43] has reported some improvement after thiamine treatment for several months as indicated by an increase in the skin temperature.

Ryss,[33] after a thorough review of the literature, recommends administration of thiamine as a part of the "complex therapy of chronic heart failure," mainly because of the results of studies by Kryzhanovskaia.[44]

Nicotinic Acid

Iakovleva[45] reported that the administration of nicotinic acid to cholesterol-fed rabbits increases the hypercholesteremia and degree of atherosclerosis. Since the reports of Altschul et al.[46] and Parsons and Finn,[47] in 1955 and 1957, it has been well known in the Western world that massive doses of nicotinic acid tend to depress the serum cholesterol level in man and in some but not all species of animals. At present nicotinic acid, in oral doses of 1,000 to 2,000 mg. daily, is widely used in the United States to reduce the serum cholesterol level in patients and in persons without complaints but who have marked hypercholesteremia.

In Russia, clinical benefit was reported by Nesterov[48] and by Ratner et al.[49] for patients with coronary heart disease who received from 0.5 to 5 mg. of nicotinic acid four to six times daily. Ratner et al. stated that this treatment may prevent abnormal electrocardiographic responses to exercise.

Soibel[50] injected subcutaneously 5 to 10 ml. of an 0.86 per cent solution of nicotinic acid (43 to 172 mg. daily) in addition to an oral dose of 100 mg. This regimen was maintained for several weeks with 125 patients suffering from coronary insufficiency, 75 of whom reported significant subjective improvement, 36 moderate improvement, and only 10 reported little benefit. From serial electrocardiograms it was judged that 62 patients were considerably improved, 39 had a moderate improvement, the improvement was little in 17, and only six patients showed no change. The "improvements" were mainly in reduction in S-T depression; T-wave inversion and arrhythmias were less affected. Serum cholesterol was not reported but it was stated that the prothrombin time was increased in some patients.

In the Russian literature up to the time of writing this review (March 1961) massive dosage of nicotinic acid as used in the United States has not been studied, and it is obvious that treatment with nicotinic acid is considered to be in the experimental stage. It is not generally recommended as a part of the treatment of patients with the clinical complications of atherosclerosis.

Pyridoxine (Vitamin B_6)

The development of arterial lesions, quite different from spontaneous human atherosclerosis, was reported a dozen years ago in the United States in monkeys and dogs fed diets grossly deficient in pyridoxine (Rhinehart and Greenberg).[51, 52] Suggestions that this may have some bearing on human atherogenesis have been discounted by almost all workers in the West. No marked effects were found on blood cholesterol in pyridoxine deficiency in dogs or various species of monkeys.[53] Parenteral administration of 25 mg. of pyridoxine daily to rabbits did not alter the serum cholesterol level. Recently, Sheikh-Ali[54] reported moderate decreases of serum cholesterol in the majority of 18 patients with coronary heart disease who received intravenous injections of 50 to 200 mg. of pyridoxine.

There has been little interest in Russia on

this subject, judging from the literature, and it is not considered in the treatment of patients with coronary heart disease.

Vitamin B_{12}

Considerable interest in the effect of vitamin B_{12} on atherosclerosis has developed recently in Russia. Lukomskii[55] gave 20 gamma of vitamin B_{12} daily for 10 days to each of 18 patients with coronary heart disease and reported an average decrease of 23 mg. per 100 ml. in the serum cholesterol concentration, associated with a small decrease in the beta lipoproteins in the serum. The effect was stated to be enhanced when choline was given simultaneously. Motovilova[56] injected larger doses (50 gamma daily) for 10 days in 40 patients, and obtained an average fall of 18 mg. of cholesterol per 100 ml. of serum. We have analyzed the data statistically and find this small change is significant ($p = 0.003$).

The effect in Motovilova's patients was stated to be maintained for 2 months and to be accompanied by reduced frequency and severity of angina "in the majority" of the patients. Further it is stated that the electrocardiogram improved in some patients and became "normal" in five of them. Specific detailed data were not given on the clinical findings.

Fomina[57] provided a treatment consisting of injection of 30 to 50 gamma of vitamin B_{12} alternating every other day with 15 to 25 mg. of testosterone. It is stated that among 43 patients with coronary heart disease, angina pectoris disappeared in 26, and 29 patients showed a decrease in the serum cholesterol level, which averaged 62 mg. per 100 ml. in these patients. Five patients had increased serum levels (average + 36 mg. per 100 ml.), and there was no change in three patients. Our calculations indicate that the distribution of these cholesterol changes, i.e., the greater frequency of a decrease, is statistically significant. No studies were made on testosterone and vitamin B_{12} separately.

The effect of vitamin B_{12} in rabbits fed 200 mg. of cholesterol per Kg. daily was studied by Ignatova,[58, 59] who reported reduced hypercholesteremia and delayed atherogenesis. When the cholesterol feeding was discontinued after 105 days, the regressive changes were followed with two groups of nine rabbits each roughly matched in regard to serum cholesterol level.[60] The serum cholesterol concentration in the control group fell from 787 to 285 mg. per 100 ml. in 112 days, while the value in the group receiving vitamin B_{12} fell from 740 to 142 mg. per 100 ml. Individual data and statistical analysis are not reported but it seems probable that there was a significant difference between the two groups in the regression of hypercholesteremia.

Ignatova[59] made planimetric measurements of the areas of the lesions in the aortas stained with Sudan III and examined sections of the walls microscopically from which it was concluded that the severity of the atherosclerosis was considerably greater in the control rabbits than in the rabbits treated with vitamin B_{12}.*

On the basis of these results, Miasnikov[28] recommends the use of vitamin B_{12} in a dosage of 0.6 mg. every second day for 2 to 4 weeks for prevention and treatment of atherosclerosis, though he indicates that clinical experience is as yet too limited for conclusive evaluation. Motovilova[56] found the prothrombin content of the blood increased in 11 out of 23 patients treated with vitamin B_{12}. Statistical analysis of her results shows an average increase of 10 per cent in the blood prothrombin, and this was statistically highly significant. It may appear, therefore, that treatment with vitamin B_{12} would be questionable unless combined with anticoagulant treatment.

Choline

In the Russian literature on treatment of patients with atherosclerosis choline is considered together with vitamin therapy.[28, 32, 55] In the Western World enthusiastic reports,

*In her latest study, Ignatova[70] found that daily intramuscular injection of 100 gamma vitamin B_{12} for 2 weeks in 75 patients with coronary atherosclerosis decreased the blood cholesterol by about 20 per cent on the average. We found the distribution of decreased cholesterol in 69 of 75 patients statistically significant. Changes of blood coagulation occurred in some patients.

such as those of Morrison and Gonzales,[61] about patients treated with choline have been largely discounted because of the absence of adequate controls and the finding of negative results of choline supplements on serum cholesterol in rabbits,[62] and man.[63] It will be recalled also that long ago Best and Rideout[64] reported that, though choline is effective in preventing the accumulation of neutral fat in the livers of rats fed cholesterol, it has far less effect in preventing cholesterol accumulation.

Pushkar[65] reported that the addition of 400 mg. of choline to the daily diet of rabbits fed 200 mg. of cholesterol, did not affect the serum cholesterol level but did delay atherogenesis. Sinitsina[66, 67] found a decrease in the serum cholesterol level as well as reduced atherosclerosis in the cholesterol-fed rabbit. In two groups of 21 rabbits each fed cholesterol for 4 months, the mean value was 1,033 mg. per 100 ml. in the control group but only 615 in the group that had received, subcutaneously, 300 to 400 mg. of choline per Kg. of body weight. Our computations indicate that this difference was significant at the level of $p = 0.05$. Sinitsina[67] also reported that the regression of atherosclerosis after discontinuance of cholesterol feeding is accelerated by choline treatment.

Koropova[68] found a tendency for the blood cholesterol to fall in 20 patients with coronary heart disease who received, by mouth, 5 Gm. of choline daily for a month. With continued choline dosage in 39 patients for a year, Koropova found that the cholesterol level was decreased in only nine patients, increased in two, and was unchanged in the other 28 patients. Subjective improvement was reported but this may have been the result of suggestion, according to Miasnikov.[28]

P. M. Savenkov (reported by Lukomskii[55]) gave 5 to 6 Gm. of choline by mouth daily for 3 weeks to 68 patients with coronary heart disease. Angina pectoris was reported by 35 patients to be significantly reduced, 18 patients said they were slightly improved, 11 patients noted no change, and one patient said he was worse. The serum cholesterol concentration fell, on the average, 40 mg. per 100 ml. in 53 of the 68 patients, a decrease of 15.6 per cent from the initial level. The serum cholesterol level rose in 15 patients, and 11 of these patients had had serum cholesterol values of 200 mg. per 100 ml., or less, before the treatment. Every patient whose initial cholesterol level was over 250 showed a decrease with choline treatment. In 26 of these hypercholesteremic patients measurements were made of the beta lipoproteins in the serum. All showed elevated values before treatment and these fell with treatment in 20 of the 26 patients. Van Chii[35] did not find consistent changes of prothrombin and fibrinogen in 38 patients treated with choline (5 Gm. per day) for 10 days.

There is a suggestion in the Russian literature that atherosclerosis is associated with a deficiency of choline or an abnormality in its metabolism. Anisimov[69] studied the blood choline content in 21 patients with coronary heart disease and in 33 control subjects. A subnormal level of choline in the blood was found in 11 of the 21 patients and this rose on a daily diet providing 73 Gm. of protein, 53 Gm. of fat, 334 Gm. of carbohydrate, and 1.5 Gm. of choline. It will be noted that this is a low-fat diet (22 per cent of total calories from fats) but we do not know how far it is below the fat content of the usual Russian diet or what other differences were involved.

Lukomskii[55] recommends choline administration for the prevention and treatment of atherosclerosis but stresses the necessity for repeated courses of treatment over a long time. The extent to which this treatment is actually used in Russia at present is not clear from the literature.

General Comment

Some of the characteristics of Russian medical research will have been indicated by this review. There is much eagerness to find effective methods of treatment, and a hopeful attitude is evident about medication such as with vitamins. Ascorbic acid is accepted as a standard part of the treatment of patients with coronary heart disease, though it is impossible to judge how many patients actually receive

this therapy. According to Miasnikov[28] it is widespread. It appears likely, too, that treatment with vitamin B_{12} will receive acceptance. It is curious, however, that massive dosage with nicotinic acid, currently so popular in the United States, has as yet been given little attention in Russia.

The possible mechanisms involved in the reported effects of the vitamins are discussed at length by Russian authors but a presentation of these considerations, some quite speculative, would require far more space than is appropriate to a review devoted to the basic clinical and experimental reports. Obviously, the reports reviewed here require careful consideration. Repetition of some of the studies, with more attention to controls and statistical analysis would be essential for critical evaluation. The great contributions of the pioneering work in Russia on atherosclerosis are obvious to all, and we may be sure that valuable research will continue in that country.

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BOOK REVIEWS

Systemic Lupus Erythematosus. *Daniel L. Larson,* Boston, Little, Brown and Company, 1961, 212 pages. $7.50.

Systemic Lupus Erythematosus reviews the experience of the Presbyterian Hospital in New York City with this disorder. Dr. Larson has analyzed the available clinical and laboratory information in 200 cases of systemic lupus erythematosus, and correlated this wherever possible with pathologic material. This monograph, then, provides an up-to-date summary of the clinical picture of this important disease, presented clearly and concisely. Its strongest feature is an excellent summary of current concepts about the L-E cell factor.

Inevitably the reader is drawn to compare this series of cases with that collected by Harvey and his associates at the Johns Hopkins Hospital. In most respects, the data obtained by the two groups are comfortably similar. Certain differences are of interest. Only nine of the 200 patients in the New York series were males, in contrast to 22 per cent in Baltimore. One wonders if the same diagnostic criteria were used by both groups. Larson emphasizes the occurrence of chronic ulceration of the legs and relates this complication to the presence of Raynaud's phenomenon and cryoglobulinemia. Harvey makes more of the myocardial lesions that may be found at autopsy. Neither group is impressed with the relationship between lupus and the lesion described by MacKay as lupoid hepatitis. Still, one does see a rare patient in whom postnecrotic cirrhosis seems an incident in the course of systemic lupus.

The Presbyterian Hospital series is notable in that 20 of the 200 patients had the nephrotic syndrome; indeed, among 48 adolescent and adult females with the nephrotic syndrome, 17 had systemic lupus erythematosus. Larson minimizes the significance of cytoid bodies in the retina in systemic lupus, a finding that was of great diagnostic help in Harvey's experience. One wonders what would have been found in Larson's series if more thorough studies of the hemostatic mechanisms had been performed. It is hard to believe that the prolonged clotting time in case 6, to quote one example, was unassociated with the circulating anticoagulant as stated.

If this monograph has a weakness, it is in the vagueness of its therapeutic recommendations. Of course, this mirrors the present state of the problem. This lively monograph is recommended as an eminently readable review of the clinical picture of systemic lupus erythematosus.

OSCAR D. RATNOFF, M.D.

Prosthetic Valves for Cardiac Surgery. Editor-in-Chief *K. Alvin Merendino.* Springfield, Illinois, Charles C Thomas, Publisher, 1960, 586 pages, illustrated. $8.25.

This book, a transcript of a conference on Prosthetic Cardiac Valves, sponsored by the United States Public Health Service, accomplishes the purpose of being an exciting documentary review of efforts and accomplishments in repairing and replacing abnormal heart valves. The volume is a record of scientific interchange on an important phase of laboratory and clinical research, the goal being the solution of problems attending the use of prosthetic heart valves.

One of the five sections of the book is devoted to materials, designs, and testing methods of prosthetic valves. Detailed descriptions of anatomic and functional concepts of aortic and mitral valves are given which represent significant enlargements upon standard textbook fare. Based upon these concepts a variety of mechanical valves have been fashioned which have functioned satisfactorily in animals and in human beings. Other sections of the book discuss myocardial metabolism and function, which must be supported to permit biologic success, and thrombus formation, which must be thwarted.

The format and quality of the text and illustrations are commendable. Bibliographies are appended to the formal presentation. There is no index.

Fact and controversy are presented with equal verve. Experience of the reader will help, but will not always permit separation of naive from sophisticated concepts. Further experiences by some of the investigators will alter concepts they espoused in 1960.

The book is recommended for all school, hospital, and departmental libraries in which the personnel are concerned with the study and treatment of cardiac valve disease. The modest cost of this compendium of current work will encourage many individuals to own and study the book. It is likely that a review of the progress reported in this

book will draw to the attention of certain physicians and surgeons that some of their patients are candidates for corrective cardiac surgery at this time.

ROY H. CLAUSS, M.D.

Clinical Disorders of the Pulmonary Circulation. Edited by *Raymond Daley, John F. Goodwin,* and *Robert E. Steiner.* Boston, Little, Brown and Company, 1960, 364 pages, 133 illustrations. $8.50.

The past decade has witnessed great strides in identifying and interpreting abnormalities in the pulmonary circulation. The effects of pulmonary disease in the aging population leading to cor pulmonale and other vascular disorders, the effects of valvular and congenital heart disease that lead to serious functional and persistent anatomic changes have stimulated important investigations. This volume offers a timely, comprehensive review of the subject. The 14 chapters deal with the entire gamut of disorders of the pulmonary circulation. These include chapters of the anatomy, physiology, radiology, and pathology of the lung and its blood supply, electrocardiography, mitral valvular and left atrial disease, and congenital heart disease. The volume concludes with several chapters dealing mainly with the pathologic physiology and clinical aspects of chronic pulmonary disease, pulmonary vascular obstruction, and pulmonary edema.

The three editors and the six guest contributors, all British, are to be congratulated on their lucid, concise surveys of the considerable literature on each of the aspects reviewed. The format is excellent and is enhanced by an adequate index, 133 illustrations, and ample documentation with references for each of the 14 chapters. This volume is heartily recommended to all physicians, particularly to cardiologists, internists, and senior medical students.

HERRMAN L. BLUMGART, M D.

Heart Sounds and Murmurs. *P. A. Ongley, M. B. Rappaport, Howard B. Sprague,* and *A. S. Nadas.* New York and London, Grune & Stratton, Inc., 1960, 316 pages, illustrated. $9.75.

The first hundred pages of this attractive book lay the foundation for the following 250 by recounting the history of the stethoscope, the characteristics of the human ear in auscultation, and a description of heart sounds, murmurs, and noncardiac chest sounds. Discussion of the acoustic stethoscope occupies an entire chapter; full consideration is given to the open bell versus the diaphragm chest piece, the effects of tubing dimensions, and improper fitting of the stethoscope to the ears.

A much longer chapter is devoted to a discussion of the combined amplifying stethoscope, the phonocardiograph-electrocardiograph, and the sphygmograph. There is a careful description of each important component part of these systems, and a full discussion of the influence of various factors encountered in their use. The fact that the bibliography of this one chapter contains 164 references may indicate something of its scope and complexity. A chapter upon the graphic registration of normal heart sounds completes the first section of the book. A second section considers heart sounds and murmurs, and a third gives specific attention to each of the four cardiac valves. The last three sections discuss rheumatic heart disease, congenital heart disease, and miscellaneous conditions.

For those who have little or no technical knowledge of the principles involved in the construction and operation of amplifying stethoscope combinations and the recording of simultaneous phonocardiograms and electrocardiograms, the 36 pages of Chapter 6 may prove difficult. The present reviewer feels no shame in confessing that he could scarcely qualify as an expert in these matters, even after several careful readings of the chapter. Let it be said immediately that this is the one really difficult section of the book for those who lack specialized training.

The section on heart sounds and murmurs contains detailed and illuminating discussions, strengthened and clarified by beautiful illustrations. The various kinds of gallop rhythm are clearly defined and illustrated. One section of almost 60 pages contains a detailed discussion of the sounds and murmurs characteristic of diseases of each of the cardiac valves. The section on congenital heart disease provides separate discussions and illustrations of 12 different malformations. The final chapter is concerned with arrhythmias, constrictive pericarditis, systemic arterial hypertension, and syphilitic aortitis with aortic insufficiency.

The great distinction of the authors is of itself a sufficient guarantee that the views expressed are authoritative. Unfortunately, Mr. Rappaport did not live to see the publication of the five chapters that he contributed. Dr. Ongley displays impressive mastery of the technical procedures and the interpretation of graphic records. The collaboration of such eminent cardiologists as Dr. Sprague and Dr. Nadas ensured that the clinical discussions and the application of photographic records to clinical problems would be of the highest possible order.

A special word of praise should be given for the beautiful illustrations (211 of them, and all perfect!), for the extensive bibliographies, and

for the superb proof-reading. This reviewer detected only one misspelled word, and no errors of punctuation!

To those who wish to increase their knowledge and understanding of heart sounds and murmurs, and to those who desire greater familiarity with modern methods of recording them, this book is warmly commended.

H. M. MARVIN, M.D.

Quantitative Vectorelectrocardiography. *Louis Brinberg,* M.D. Baltimore, Waverly Press, Inc., 1960, 123 pages, illustrated. $5.25.

This interesting volume concerned primarily with the application of a variety of mathematical and geometric technics to vectorcardiography is a compilation of a series of articles by the author which have appeared in the literature in the last 4 years. There are seven chapters concerned with such mathematical matters as the principles of orthographic projection; the determination of spherical coordinates of a vector in space from its horizontal projection and horizontal revolute (the latter pair when applied to successive vectors being called the orthovectorcardiogram); the use of principles of spherical trigonometry and navigation in the analysis of the electric forces produced by heart muscle. Of particular interest to the vectorcardiographer is the method of obtaining the magnitude, azimuth, and elevation (M°, H°, and V°) of spatial instantaneous vectors from the horizontal projection and from the Lissajoux figure in which the termini represent the true vector magnitudes and their elevations ("horizontal revolute").

The chapter on the use of the sphere for describing vectors in terms of longitude and latitude, bearing and position, will familiarize the reader with some terms used by navigators and cartographers. Some new terms have been introduced such as the plane of mean ventricular activity (Pl_v), the slope of this plane, the triangle of the independent forces, the spherical vectorcardiogram, and the plane of QRS (Pl_{QRS}). In addition, there are presented a variety of mathematical schemes for representing planes, loops, tortuosity, and velocity of the spatial cardiac vector.

There are some interesting treatments of the use of the spherical surface as being most suitable for the application of statistical technics to groups of spatial axes. Some data are given on the calculation of the QRS-T angle made from a spherical surface, and this is developed further in the chapter concerned with the three-dimensional statistical technics for comparing, for example, ventricular gradients each represented as a single measurement.

A discussion of the lead vector is illuminating as far as it goes but does not include the significance of direction of this vector as well as magnitude. A lengthy analysis of the ventricular gradient is lucid and should be of some value to those who do not have a solid grasp of this concept. There might be some difference of opinion on including the area of the P wave in any method of measuring the ventricular gradient insofar as the author has assumed from work done elsewhere that a gradient as such does not exist in the atria and that the area of P balances the area of T_P. In the last chapter some mathematical tricks are shown for obtaining the angles subtended by a spatial vector on the three cardinal planes and three cardinal axes.

This book is carefully written but is slightly repetitious. It gives one the impression that Dr. Brinberg has a fine background in solid geometry and related fields. He makes no attempt to solve such problems in man as what are the true X, Y, and Z axes, what are the lead vectors, and how inaccurate it is to assume that the torso simulates a sphere. However, some information is given on mean values of various vectors obtained in normal man either by the conventional electrocardiographic leads or by the cube reference frame for vectorcardiographic leads. Correctness of the title of the book might be questioned. Perhaps more appropriate though less succinct would be "Methods of Analysis and Description of Spatial Forces as Applied to Vectorcardiography."

It certainly should be of use to those in the field of vectorcardiography, for it does elaborate in an exact way the various mathematical means by which spatial forces may be handled descriptively and statistically.

CHARLES E. KOSSMANN, M.D.

Congenital Malformations of the Heart. I. General Considerations. II. Specific Malformations. *Helen B. Taussig.* Cambridge, Published for the Commonwealth Fund by Harvard University Press, 1960; Vol. I, 204 pages, $4.75; Vol. II, 1,049 pages. $17.50.

Few areas of medicine have been characterized by such rapid progress as the diagnosis and treatment of congenital malformations of the heart. It is consequently fortunate that the formidable task of assessing the present status of this field has been undertaken by such an outstanding authority. The first edition of this classic was published in 1947.

In the foreword of this new two-volume edition, the author felicitously states: "This edition is like a deciduous tree: the fundamental outline of the tree remains, but the tree has all new

leaves and a few new branches. As a tree grows and bears fruit, so it is hoped that this book will enable others to further extend our knowledge." Several chapters have been added including discussions of pulmonary hypertension, the Taussig-Bing malformation, defective development of the right ventricle with an intact ventricular septum, and aortic septal defect. Every chapter has received extensive painstaking revision.

Volume I emphasizes the basic concepts and methods employed in the diagnosis of congenital malformations, particularly physical examination, x-ray, fluoroscopy, and angiography, electrocardiography, cardiac catheterization, and other special procedures. The discussion of the general principles of diagnosis is preceded by a superb chapter on embryology, etiology, principles of analysis of data, and description of the fetal circulation.

The final chapter of this slim first volume of 200 pages is concerned with the medical care of these patients. The author wisely observes: "As an ever increasing number of malformations can be helped by surgery, it becomes of real importance not only to enable these children to survive until the optimum age for surgery but also have them grow to be well-adjusted, useful citizens. Experience has shown that the better adjusted a child is prior to operation, the more easily and the better he adjusts to society after operation. Fear of death should never be permitted to enter his mind. Self-pity should not be allowed. The child should be treated with the confident expectation that he will live to grow up and become a self-supporting citizen." The remainder of the chapter explicitly advises the physician regarding exercise, rest, posture, education, immunization, dental care, tonsillectomy, anesthesia, bacterial endocarditis, problems related to persistent cyanosis, and all the numerous cardiac complications such as the management of congestive heart failure and of the cardiac arrhythmias.

Volume II provides detailed information on each of the specific malformations. They are grouped in four categories as follows: malformations with a venous arterial shunt, malformations on the right side of the heart with or without a venous-arterial shunt, malformations in which the primary shunt is from left to right, and malformations of the left side of the heart. The volume is concluded with an ingenious display of a series of plates that succinctly portray the patient's age, sex, activity, characteristic murmurs, and electrocardiogram of the principal malformations.

The vast accumulation of knowledge in the two volumes is made readily accessible by an excellent index in each volume. Dr. Taussig's exceptional qualities are manifest throughout. As Dr. Edwards A. Park remarks in his foreword: "Dr. Taussig reaches her conclusions by gathering meticulously all the facts pertaining to the case and fitting them together in their proper relations by a process of clear, logical thinking carried through to the very end. Her conclusions seem inescapable when her evidence is presented. In her text on the malformations of the heart she has given as much of her scholarship as is possible to convey in that brief form; moreover, wherever possible, she has simplified her difficult task of exposition through the use of diagrams which give visual explanations of conditions extremely difficult to describe in words. By means of this book the diagnosis of malformations of the heart is brought within the power of all physicians who are willing to devote time to its study and to practice its teachings."

The format is superb, particularly the illustrations and diagrams. These two volumes published for the Commonwealth Fund by the Harvard University Press are the definitive reference on the subject for all physicians.

HERRMAN L. BLUMGART, M.D.

Surgery of the Aorta and Its Branches. *James D. Hardy.* Philadelphia and Montreal, J. B. Lippincott Company, 1960, 386 pages, 75 illustrations. $6.50.

Dr. Hardy has presented an excellent survey of a rapidly expanding branch of surgery. There is sufficient emphasis on basic pathologic processes and surgical principles so that in spite of frequently changing technics much in this book will probably be acceptable for many years to come.

The subject matter is all inclusive. An extensive bibliography follows each chapter. Presentation is concise. The book is recommended for surgeons predominantly, may be of interest to our medical colleagues but may be somewhat incomplete for those who do predominantly vascular surgery.

ANTHONY M. IMPARATO, M.D.

Blood Flow in Arteries. *Donald A. McDonald.* Baltimore. The Williams & Wilkins Company, 1960, 328 pages, illustrated. $8.50.

"Blood Flow in Arteries" ties together many hitherto unrelated facts associated with hemodynamics. It is apparently written for the physiologist and research physician. The book for the most part is written from a non-mathematical point of view. At certain points the complexity of the mathematics appear to be out of "character" with the general level of the book.

It has truly taken an engineering approach to this matter in a most logical and interesting manner.

The general aspects of laminar and turbulent flow with respect to Newtonian fluids are noted and the effect of pulsations imposed on flow is discussed.

The viscosity characteristics of blood were only briefly mentioned. A more detailed discussion of this topic would have been appropriate.

The various methods for measuring blood flow rates were described and compared.

Whenever it was appropriate engineering considerations were clearly noted and applied to vessel walls, pulsating flow, and disturbances in flow.

There are a number of relatively minor errors that appear: on p. 14, p. 16, reference is made to the fact that as tube diameter decreases, the flow becomes more stable (assuming a constant rate of flow). Actually, for circular tubes the Reynold's no. is $\frac{4W}{\pi Du}$ (where W is mass rate of flow). Therefore as a tube tapers or diameter decreases, the Reynold's no. becomes greater and flow becomes less stable. On page 38, mention is made of the fact that plasma, although a colloid solution behaves as a Newtonian fluid. Studies with cone and plate viscometers indicate that this may not be the case with respect to plasma that has been obtained from blood not treated with anticoagulants. On page 49, the author notes that it is difficult to conceive in flowing blood there can exist at the same time a turbulent "sleeve" of plasma with a laminar central "cone." Actually, this condition has been noted to occur in the pumping of paper pulp. The technic used for determining the critical Reynold's no. in paper pulp flow might be more appropriate for ascertaining the conditions for turbulent flow in blood than the methods presently employed.

This book serves the important function of introducing the engineering approach to hemodynamics as well as acquainting the reader with the varied aspects of a hemodynamic system.

STANLEY E. CHARM, Sc.D.

Demonstrations of Physical Signs in Clinical Surgery. *Hamilton Bailey.* Baltimore, Ed. 13. The Williams & Wilkins Company, 1960, 928 pages, 1142 illustrations. $14.50.

This voluminously illustrated book is, in the words of the authors preface, "written originally for the student commencing clinical work in the surgical wards and the out-patient department." Primary emphasis is placed upon the formulation of a diagnosis by means of the history and physical examination and little space is devoted to the ancillary x-ray and laboratory findings in specific syndromes.

The initial chapters deal with a number of fundamental states seen in surgical patients and a recapitulation of basic physical signs. The author then proceeds to examine the various organ systems and topographic areas of the body describing and illustrating the pathologic entities amenable to diagnosis by physical examination. Numerous artist's illustrations are used to clarify those situations that cannot be faithfully and completely shown by photographs. The caliber of the illustrative work is excellent throughout the entire book.

In summary this book represents a comprehensive outline of basic physical findings for the initiate in surgery. It's format, composition and typography are excellent. It appears designed for the medical student or for the surgeon desiring an illustrated review of physical signs.

PETER W. STONE, M.D.

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Surgical Management of Mitral Stenosis. *Robert P. Glover* and *Julio C. Davila.* New York, Grune & Stratton, Inc. 1961, 219 pages, illustrated. $9.50

Index-Handbook of Cardiovascular Agents. Vol. II. Parts I and II. *Issac D. Welt.* Washington, D. C., National Academy of Sciences, National Research Council, Publication 821, 1,568 pages. $15.00.

Systemic Lupus Erythematosus. *Daniel L. Larson.* Boston, Little, Brown and Company, 1961, 212 pages. $7.50.

Management of Hypertensive Diseases. *Joseph C. Edwards.* St. Louis, The C. V. Mosby Company, 1960, 439, pages, illustrated. $15.00.

Prosthetic Valves for Cardiac Surgery. Editor-in-Chief *K. Alvin Merendino.* Springfield, Illinois, Charles C Thomas, 1960, 586 pages, illustrated. $8.25.

Medical and Biological Research in Israel. Edited by *Moshe Prywes.* New York, Grune & Stratton, Inc., 1960, 562 pages, illustrated. $8.00.

Cardiopericardiomyopexy. New Surgical Treatment for Heart Diseases. *Aaron N. Gorelik and his associates.* Revised English Edition of "La Cardiopericardiomyopexie," Paris, Expansion Scientifique Francaise, 1956, 176 pages, 30 figures.

Haematology. *R. B. Thompson.* Philadelphia, J. B. Lippincott Company, 1961, 306 pages, 27 figures. $6.00.

Cardio-vascular Surgery. A Manual for Nurses. Members of the Surgical Staff and Members of the Nursing Service Staff, The Methodist Hospital, Houston. Edited by *George H. Peddie and Frances E. Brush.* New York, G. P. Putman's Sons, 170 pages, illustrated.

Metabolic Effects of Adrenal Hormones. Ciba Foundation Study Group No. 6. Edited by *G. E. W. Wolstenholme and Maeve O'Connor.* Boston, Little, Brown and Company, 1960, 109 pages, illustrated.

Drug Action on Adrenergic Mechanisms. Ciba Foundation Symposium. Editor for the British Pharmacological Society, *J. R. Vane.* Editors for the Ciba Foundation, *G. E. W. Wolstenholme and Maeve O'Connor.* 1960, 632 pages, 163 illustrations. $12.50.

New Soviet Surgical Apparatus and Instruments and Their Application. Edited by *M. G. Anan'yev.* Translated from the Russian by *John Barry Elliott.* Translation edited by *David Brooks.* New York, Pergamon Press, 1961, 222 pages. $12.50.

Essential Hypertension—An International Symposium. Chairman F. C. Reubi, Edited by *K. D. Bock* and *P. T. Cottier.* Berlin, Springer, Verlag, 1960, 392 pages, 81 figures. DM 152.

Circulatory Ulcers. A Physical Approach. Edited by *Hilton Tranchell* and *Charles Bannister.* Bristol, John Wright & Sons Ltd., 1960, 91 pages, 16 figures. $3.50.

Blood Platelets. Edited by *Shirley Johnson, Raymond Monto, John Rebuck,* and *Robert Horn.* Boston, Little, Brown and Company, 1961, 732 pages, illustrated. $18.50.

Die Dynamik des venösen Rückstromes. Edited by *Henner Krug* and *Ludwig Schlicher.* Leipzig, Georg Thieme, Verlag, 1961, 240 pages, 41 figures. DM 34, 55.

Symptom Diagnosis. Edited by *Wallace Mason Yater* and *William Francis Oliver.* New York, Appleton-Century -Crofts, Inc., 1961, 951 pages. $15.00.

Disease and Injury. Edited by *Leopold Brahdy.* Philadelphia, J. B. Lippincott Company, 1961, 482 pages. $12.50.

Stress and Your Heart. Edited by *Fred Kerner.* New York, Hawthorn Books, Inc., 1961, 237 pages. $4.95.

Coronary Vasodilators. Edited by *R. Charlier.* New York, Pergamon Press, 1961, 215 pages, 24 figures. $8.50.

A Prelude to Medical History. Edited by *Félix Martí-Ibáñez.* New York, MD Publications, Inc., 1961, 253 pages. $5.75.

Varicose Veins. A Practical Manual. *R. Rowden Foote.* Bristol, John Wright & Sons Ltd. 1960, 355 pages, 304 illustrations. $13.00.

Simplified Diet Manual. Ed. 2. Prepared by Nutrition Service of the Iowa State Department of Health in Cooperation with the Iowa Dietetic Association. Ames, Iowa State University Press, 119 pages. $2.50.

The Peripheral Circulation of Blood, Lymph and Tissular Fluid. *C. D. De Langen.* Haarlem, De Erven F. Bohn N. V., 1961, 165 pages, 7 illustrations.

Das Röntgenbild des Herzens. *D. Routier.* Stuttgart, Georg Thieme, Verlag, 1961, 69 pages, 16 figures. DM 5.80.

The Cardiac Arrhythmias. *Brendan Phibbs.* St. Louis, The C. V. Mosby Company, 1961, 128 pages, 91 illustrations. $7.50.

Quinones in Electron Transport. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme,* and *Cecilia M. O'Connor.* Boston, Little, Brown and Company, 1961, 453 pages, illustrated. $11.00.

Virus Meningo-Encephalitis. Ciba Foundation Study No. 7. Edited by *G. E. W. Wolstenholme,* and *Margaret P. Cameron.* Boston, Little, Brown and Company, 120 pages, 11 illustrations.

Hypertension. *Milton Mendlowitz.* New York, Grune & Stratton, Inc., 1961, 156 pages, illustrated. $6.50.

Praktische Hämatologie. *H. Begemann* and *H. G. Harwerth.* Stuttgart, Georg Thieme, Verlag, 1961, 298 pages, 28 illustrations. $8.25.

Cardiology. Vol. 5. *Aldo A. Luisada.* New York, McGraw-Hill Book Company, Inc., illustrated. $27.50.

Clinical Haematology. *Robert Duncan Eastham.* Bristol, John Wright & Sons Ltd., 158 pages. $4.00.

ABSTRACTS

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CORONARY ARTERY DISEASE

Blomqvist, G., Sievers, J., and Biorck, G.: Studies on Myocardial Infarction in Malmo 1935 to 1954. V. Recurrent Infarction. Incidence and Immediate Mortality. Acta med. scandinav. 167: 331, 1960.

The population studied was 970 patients who survived 4 weeks after a clinically primary myocardial infarction. There were 620 men and 350 women. These patients were all hospitalized during the period 1935 to 1954. One hundred sixty-two recurrent infarctions occurred over a period of 3,278 "person-years" of observation. The material was divided by sex and by age (above or below 60). The incidence of recurrent infarction was estimated per 100 "person-years" of exposure to risk during various periods after the primary infarction. This was termed "force of recurrence." Long-term anticoagulants were employed in the occasional patient and exclusively during the last few years of the study, but the authors believe that this did not affect the material appreciably. The force of recurrence among patients below 60 was higher in men than women; and the opposite was true for patients over 60. The over-all force of recurrence for men was the same as it was for women. The immediate mortality was not significantly different for the primary infarction, those patients with one previous infarction, and those with two or more previous infarctions. In general, the risk of experiencing a recurrent infarction was higher during the first year after the initial attack than later. In males below 60 years of age, the highest frequency tended to be within the first 6 months. For all other subgroups, the opposite was true; but in the material as a whole, the difference between the first and second half-year period was negligible. The force of recurrence in patients under 60 during the first year after primary infarction was 7.9; for patients over 60, 9.9.

SHEPS

Carleton, R. A., Sanders, C. A., and Burack, W. R.: Heparin Administration after Acute Myocardial Infarction. New England J. Med. 263: 1002 (Nov. 17), 1960.

Of 81 patients with acute myocardial infarction 41 were randomly selected to receive heparin every 6 hours through an indwelling catheter. The remaining 40 were not given anticoagulants. Comparison of the two groups showed no significant difference in the hospital course, the incidence of thromboembolic complications, and the death rate. It was concluded that this study showed no beneficial effect from heparin during convalescence from acute myocardial infarction, and, therefore, that heparin at the present time cannot be recommended for routine use as the only anticoagulant during the treatment of an acute myocardial infarction.

SAGALL

Carlson, L. A.: Serum Lipids in Men with Myocardial Infarction. Acta med. scandinav. **167:** 399, 1960.

Serum lipids and lipoprotein concentrations were studied in 49 men with myocardial infarction and in normal men. The basis for separation into age groups was the age at which the myocardial infarction occurred and not the actual age of the patient at the time of the study. In men who had a myocardial infarction before the age of 50, the serum glycerides were found to be elevated to a greater extent than the serum cholesterol. The reverse was true at an older age group. The cholesterol/phospholipid ratio was not significantly altered. The high-density lipoprotein had relatively low concentration of cholesterol and phospholipids, especially in the younger age group. The low-density lipoprotein content of cholesterol and phospholipids was elevated. The concentration of glyceride was greatest in those lipoproteins with a ratio of cholesterol to phospholipid below 1. This was usually in the low-density lipoproteins. On the other hand, in men with the myocardial infarction after the age of 50, there was an increase in lipoprotein with a higher content of cholesterol than of phospholipids and with a low content of glycerides. This type of lipoprotein would best correspond to the low-density lipoproteins. The author concludes that in men who sustain a myocardial infarction under the age of 50 there is a disturbed metabolism of the serum glyceride, whereas in the older age group, the main abnormality is an altered metabolism of serum cholesterol.

SHEPS

Chazov, E. I.: New Findings on the Origin of Thrombosis of the Coronary Arteries. Cor et Vasa **2:** 169, 1960.

Intravenous injection of thrombin, in doses that did not produce thrombosis when injected alone, led to coronary thrombosis and electrocardiographic signs of coronary insufficiency when combined with 0.5 ml. of pituitrin, which alone was ineffective, in 17 of 21 rabbits. Of 31 rabbits on a high-cholesterol diet, animals who had been on the diet 110 to 120 days and developed marked coronary lipoidosis reacted to intravenous thrombin with coronary thrombosis and electrocardiographic signs of myocardial infarction; animals on the diet for 70 to 80 days showed these changes after thrombin only when accompanied by pituitrin. Rabbits with experimental coronary thrombosis showed a smaller reactive increase to heparin and fibrolysin after thrombin injection than normal rabbits; a similar though smaller decrease in the compensatory reaction was observed after vascular spasm. It is suggested that this decrease, in addition to the vascular changes, is a cause of thrombosis.

LEPESCHKIN

Dinon, L. R., and Vander Veer, J. B.: Recurrent Myocardial Infarction after Cessation of Anticoagulant Therapy. Am. Heart J. **60:** 6 (July), 1960.

Twenty cases are reported with recurrence of acute myocardial infarction developing within 4 weeks after abrupt or relatively rapid discontinuation of anticoagulation therapy. When anticoagulants were reduced gradually over a period of some weeks recurrence of acute myocardial infarction seemed to be less common. The mechanism responsible for the causal relationships between the rapid withdrawal of anticoagulants and recurrence of acute myocardial infarction, if such does exist, has not been established but may result from "rebound" hypercoagulability of the blood or the possible effects of anticoagulants on a disordered blood flow. The presently reported cases indicate the advisability of more prolonged anticoagulant therapy after clinical recovery from a first attack of myocardial infarction and further suggest that when such therapy is terminated, the dosage of anticoagulant be reduced very gradually over a period of at least 4 weeks.

SAGALL

Dressler, W., August, S., Epstein, I., and Rosenberg, B.: Pericarditis Following Mild or Silent Coronary Episodes: An Attempt at Narrowing the Field of Idiopathic Pericarditis, Am. Heart J. **60:** 12 (Nov.), 1960.

Five patients with the postmyocardial infarction syndrome of pericarditis, pleurisy, and pneumonitis are presented. It is pointed out that on occasions this so-called "coronary" pericarditis may follow a mild or silent myocardial infarction or may be quite delayed in its appearance after acute myocardial infarction, so that an erroneous diagnosis of idiopathic pericarditis is made. In any given case of pericarditis the search for the cause should include a "coronary" origin. Attention to this diagnostic possibility will reduce the number of cases assigned to the idiopathic group of pericarditis and may be a guide to effective therapy.

SAGALL

Kekki, M., and Halonen, P. I.: Studies of Plasma and Urinary Amino Nitrogen in Myocardial Infarction. Acta med. scandinav. **168:** 133, 1960.

Previous reports had indicated that the amino acid concentration in the blood was increased

following acute myocardial infarction. In 11 patients with myocardial infarction and in six control subjects the amino nitrogen concentration in the plasma was followed over a period of 3 weeks. In addition, urinary amino nitrogen and individual amino acids in the urine and plasma were also determined. The only significant finding was a suggestion of an increased amount of glutamic acid present in the plasma during myocardial infarction. No changes were found in the urine.

SHEPS

Kulpe, W., and Neuhaus, G.: Arterio-venous Fistulas of the Coronary Arteries. Ztschr. Kreislaufforsch. **49:** 689 (Aug.), 1960.

A 37-year-old man developed increasing anginal complaints and signs of congestive heart failure over the past 10 years, and showed deep Q waves with S-T elevations in leads II and III and inverted T waves in leads I and V_3 to V_6 in the electrocardiogram. The phonocardiogram showed a systolic murmur in the second left interspace and a late diastolic murmur in the third to fourth interspace at the sternal edge. Right cardiac catheterization disclosed an oxygen saturation of 52 per cent, a systolic blood pressure of 65 mm. Hg, and a diastolic of 3 mm. Hg in the coronary sinus; these values are considerably higher than normal, and allow the diagnosis of an arteriovenous coronary fistula. It was believed that the fistula was located in the region of the left circumflex or right descending branch, and had led to myocardial ischemia because of low coronary pressure near the fistula. In this case the fistula was attributed to mycotic embolism from a perinephritic abscess, which the patient developed shortly before appearance of cardiac symptoms.

LEPESCHKIN

MacMillan, R. L., Brown, K. W. G., and Watt, D. L.: Long-Term Anticoagulant Therapy after Myocardial Infarction. Canad. M. A. J. **83:** 567 (Sept. 10), 1960.

Preliminary observations of dicumarol therapy following myocardial infarction were presented. Twenty-seven patients received therapeutic doses aimed at increasing the capillary prothrombin time to 20 to 30 seconds, while 23 others received homeopathic doses—all over an average period of 13 months. Recurrent infarction occurred in six persons in the treated group and in four of the control group. There were eight deaths in the treated group, three or more due to heart disease, and none of the controls died. Abnormal bleeding was seen in eight of the treated patients and in one of the controls. Some of the reported experiences with this type of therapy were summarized and were favorable. However, the present authors concluded that the possible value of such therapy remained to be established.

ROGERS

Master, A. M.: The Role of Effort and Occupation (Including Physicians) in Coronary Occlusion. J.A.M.A. **174:** 942 (Oct. 22), 1960.

Misconceptions still prevail concerning coronary occlusion in spite of the enormous amount of research being carried on regarding it. A questionnaire method was developed for the study of 2,600 cases of proved acute coronary occlusion. The data included the hour, the day, the type of effort, or the mode of rest at the onset of the episode. The results did not incriminate occupation, exertion, or state of inactivity in the precipitation of the occlusion. There was no evidence that one attack of acute coronary occlusion predisposed to a second attack except indirectly because of the underlying atherosclerotic disease. The author does not believe that coronary occlusion has become epidemic or that it is caused by modern stress or strain. Its apparent incidence has increased because of increased age of the population, improved diagnostic skills, and changes in the classification of heart diseases. At present neither cause nor prevention of coronary occlusion is known. It is the end result of an atherosclerotic process and it occurs independently of external influences.

KITCHELL

Portsmann, W., and Geissler, W.: On Coronary Arterio-Venous Fistulas. Fortschr. Röntgenstr. **93:** 143 (Aug.), 1960.

A 41-year-old man showed an intense murmur beginning in early systole and continuing into the last half of diastole with a maximum in the fifth interspace at the sternal edge. The electrocardiogram showed incomplete right bundle-branch block. Fluoroscopy disclosed slight left ventricular enlargement and kinking of the aorta; right heart catheterization showed normal values but left ventricular catheterization from the femoral artery was suggestive of slight aortic isthmic stenosis. Aortography of the ascending aorta through the catheter demonstrated marked dilatation of the right coronary artery, which showed a wide communication with several cardiac veins. This is the forty-first case of coronary arteriovenous fistula reported in the international literature, and one of the few where diagnosis was made during life preoperatively.

LEPESCHKIN

Spain, D. M., Bradess, V. A., and Mohr, C.: Coronary Atherosclerosis in Unexplained Death. J. A. M. A. **174:** 384 (Sept. 24), 1960.

The frequency of coronary atherosclerotic heart disease as a cause of sudden unexplained and unexpected death in adults was determined in a series of 1,329 consecutive autopsies. Analysis revealed three types of "sudden death" according to the duration of the fatal episode: less than 1 hour, between 1 and 3 hours, and undetermined (unwitnessed). Where the duration of the witnessed fatal episode was less than 1 hour, coronary disease was the cause in over 90 per cent of the cases. In all other categories, coronary artery disease was the cause of death 60 per cent of the time or less. It is noted that cerebral vascular disease usually produces a terminal fatal episode that is over 1 hour in duration and is a relatively infrequent cause of "sudden death."

KITCHELL

Watson, H., Emslie-Smith, D., Herring, J., and Hill, I. G. W.: Myocardial Infarction during Pregnancy and Puerperium. Lancet **2:** 523 (Sept. 2), 1960.

Myocardial infarction was diagnosed in association with pregnancy in two young women. One, age 22, had a major anterior infarct 2 weeks from term, the other, aged only 17, had a posterior infarct 6 days after delivery. Neither had severe anemia, hypertension, diabetes mellitus, or other metabolic disorder. Previously reported cases of the coincidence of pregnancy and myocardial infarction were reviewed and their incidence was found to be widely scattered, almost equally divided between the first and second halves of pregnancy, a quarter occurred before the end of the second month at a time when the measurable alteration in lipid pattern was relatively small. Few of the patients were very young, most being 36 years old or over, and many had arterial hypertension. Of the six young patients, all but one had an infarction later in pregnancy. It is interesting that most patients survived the infarct and did remarkably well. Eight patients died; 18 survived, 8 of whom received anticoagulant therapy without ill effect even when it was used immediately after delivery.

KURLAND

Wexler, J., and Patt, H. H.: Evidence that Serum Potassium Is Not the Etiological Agent in Ventricular Fibrillation following Coronary Artery Occlusion. Am. Heart J. **60:** 618 (Oct.), 1960.

The results of 83 dog experiments in which coronary sinus blood was studied after ligation of the left anterior descending coronary artery are reported. In 69 dogs so studied an elevated concentration of potassium was found in the coronary sinus after ligation of the coronary artery in only 33 per cent and in 18 of these 23 dogs a normal sinus rhythm was maintained throughout the entire experimental period. Twelve animals developed ventricular fibrillation after coronary artery ligation, but in only three was there a significant elevation of potassium in the coronary sinus blood. In none of the 12 was there a significant elevation of potassium in the coronary sinus blood or an increase in potassium in the femoral artery blood. It is concluded that these results do not support the thesis that an increase in the levels of serum potassium incites ventricular fibrillation after coronary artery ligation.

SAGALL

Wroblewski, F., Ross, C., and Gregory, L.: Isoenzymes and Myocardial Infarction. New England J. Med. **263:** 531 (Sept. 15), 1960.

Starch-gel electrophoresis determination showed that human plasma lactic dehydrogenase activity results from the combination of five isoenzymes, designated pLD_1, pLD_2, pLD_3, pLD_4, and pLD_5. In normal adults a typical isoenzyme pattern was found, i.e., $pLD_2 < pLD_1 < pLD_3 < pLD_5 < pLD_4$. Various human tissues were found to contain one or more of these isoenzymes in combinations forming an individual and characteristic isoenzyme pattern. Heart muscle had a isoenzyme composition different from that of other tissues. Normally, it contained LD_4 and LD_5 with a preponderance of LD_5. Following transmural and subendocardial myocardial infarction the isoenzyme pattern of plasma was altered with an increase in pLD_4 and pLD_5. The characteristic pattern showed pLD_5 to be greater than pLD_4. This particular plasma isoenzyme pattern was found to be a more sensitive, a more specific, and a more lasting parameter of myocardial necrosis than the measurement of total serum or plasma enzyme activity. Furthermore, diseases of other organs that result in alterations of total plasma enzyme activity were associated with a change in the plasma isoenzyme pattern different from that observed after myocardial infarction.

SAGALL

Zipp, H.: A Case of Myocardial Infarction after an Electric Accident. Ztschr. Kreislaufforsch. **49:** 620 (July), 1960.

A 63-year-old farmer without previous cardiac symptoms received an electric shock of about 200 volts through his left hand. After 2 hours he started to feel precordial pressure that be-

came intense during the following day. An electrocardiogram showed very small R waves in leads V_2 and V_3 and deep terminal inversion of the T waves in leads V_{1-5}; this increased during the following month and disappeared after a year. It is concluded that the electric current had precipitated a thrombosis in an already arteriosclerotic coronary artery, which led to rudimentary myocardial infarction.

LEPESCHKIN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Abel, H.: The Spatial Area Vectors in Hypertensive Disease. Ztschr. Kreislaufforsch. **49**: 636 (July), 1960.

In 20 patients with hypertension the three limb leads and three orthogonal leads of the SVEC-III system (Schmitt and Simonson) were registered synchronously. The area vector of QRS showed a tendency to deviate toward the left superior posterior octant, while the ventricular gradient was diminished but remained in the left inferior anterior octant. In six patients the frontal plane gradient determined from standard limb leads was normal, while this gradient, determined from the orthogonal system, had abnormal values.

LEPESCHKIN

Blumberger, K.: Physio-pathologic and Diagnostic Significance of Subclavian and Carotid Pulse Tracings in Aortic Valvular Disease. Arch. mal. coeur **53**: 481 (May), 1960.

In aortic stenosis the carotid pulse tracing is characterized by rapid vibrations superimposed on its ascending branch, a later appearance of the summit, and reduced amplitude. In aortic regurgitation the ascending branch is steeper, the summit appears earlier, the amplitude is higher, and the incisura becomes smoother or disappears, since there is no complete closure of the valve. The femoral pulse often shows a low notch in its ascending branch. This notch is caused by the increased stroke volume, since it may appear in persons without aortic regurgitation after long diastolic pauses. In combined aortic stenosis and regurgitation the pulse wave changes partly neutralize each other, but often the diagnosis is possible, since the amplitude is elevated but the beginning or summit of the pulse wave is delayed.

LEPESCHKIN

DePasquale, N., and Burch, G. E.: The Spatial Vectorcardiogram in Left Bundle Branch Block and Myocardial Infarction, with Autopsy Studies. Am. J. Med. **29**: 633 (Oct.), 1960.

The authors present the vectorcardiographic characteristics of left bundle-branch block complicated by myocardial infarction for 15 patients whose hearts were studied at autopsy. The rotation and direction of the QRS sE-loop in left bundle-branch block complicated by myocardial infarction was similar to that seen in left bundle-branch block complicated by left ventricular hypertrophy, the QRS sE-loop being inscribed slowly to the left, superiorly, and posteriorly. With anterior infarction, the QRS sE-loop was displaced posteriorly. No characteristic vector pattern could be described for patients with left bundle-branch block complicated by posterior myocardial infarction as in all these patients other areas were also involved.

KALMANSOHN

Finardi, C.: Phonocardiographic Study of Heart Sound Amplitude Changes Caused in Subjects with Normal Cardiovascular System by Breathing a Mixture Poor in Oxygen. Arch. mal. coeur **53**:549 (May), 1960.

In 10 normal men the electrocardiogram was registered together with a stethoscopic phonocardiogram from the apical region, during, before, and after breathing of a mixture of 10 per cent oxygen in nitrogen. First as well as second heart sounds showed a progressive and reversible decrease of amplitude, which reached 50 per cent after 15 minutes of hypoxia. The heart rate and the corrected Q-T duration increased, but the duration of mechanical systole, as judged from the heart sounds, increased more than the electrical systole.

LEPESCHKIN

Friese, G., and Oppitz, M.: Observations on Rudimentary Anterior Wall Infarction. Ztschr. Kreislaufforsch. **49**:612 (July), 1960.

Terminal inversion of the T wave in leads V_2 to V_4 accompanied by low voltage or inversion of the T wave in lead I, but not by QRS changes, was seen in 88 patients or 0.084 per cent of all patients during the years 1954 to 1958. This pattern, which is attributed to rudimentary anterior myocardial infarction, showed an increase in incidence during these years; it was found more commonly in women (44 per cent) than typical anterior infarction, but the average age was exactly the same (58.8 in men, 62.5 in women) as in typical infarction. Anginal complaints in this group were less common (62 per

cent) than in typical infarction, especially in the older patients. However, 11 of the 19 patients without complaints showed marked arteriosclerosis or factors favoring its appearance. This finding, as well as the absence of other causes, which could be responsible for this pattern and its slow appearance and regression, favors its interpretation as due to small or rudimentary infarction rather than to functional changes. None of the patients died.

LEPESCHKIN

Goldman, A. G., Gross, H., and Rubin, I. L.: Transitory Q Waves Simulating the Q Wave of Myocardial Infarction. Am. Heart J. **60**:61 (July), 1960.

The problem of transitory Q waves simulating those of myocardial infarction is considered. Two patients are reported in whom significant Q waves were found in the electrocardiogram, but myocardial infarction was not demonstrated at postmortem examination. In two additional patients, a significant diminution in the area of abnormal precordial Q waves occurred within several days following acute myocardial infarction. It is concluded that when a metabolic insult is severe enough to result in myocardial electrophysiologic disturbance, Q waves may be transiently present in the electrocardiogram. Such transitory Q waves, however, despite their persistence over a period of several hours to several days do not necessarily mean that anatomic change has developed in the myocardium.

SAGALL

Haas, H. G.: A Contribution to the Theory of Ventricular Gradient. Cardiologia **36**:321, 1960.

Based on the elementary processes in a single fiber, the ventricular gradient is derived as a resulting vector that represents the relation between the R and T waves in the electrocardiogram. A formal analysis of the causes of the ventricular gradient reveals that an explanation of concordant R and T waves in the electrocardiogram cannot be based on purely geometric factors, but that a spatial inhomogeneity in the course of the action potential has to be postulated. Such inhomogeneity concerning a single fiber generally results only in some degree of deviation from the normal concordance with equal areas, but not in a reversal of direction producing concordance. Calculation based on a simple model reveals that, in these circumstances, concordance may yet result in the electrocardiogram, namely, on the assumption of a marked divergence in space of the fibers, as it is most probably present in actual fact. This demonstrates that it is certainly not necessary to assume a local concordance for certain fibers, as was the case with the global differential construction between base and apex of the heart.

BRACHFELD

Haas, H. G., Blomer, A., Ley, M., and Schaefer, H.: Experimental Investigations in Dog Heart on the Problem of Ventricular Gradient. Cardiologia **37**: 66, 1960.

Detailed observations on the spread and course of excitation in the heart were made on 27 dogs. After opening the thorax, microelectrodes were applied to the epicardial surface of both ventricles, and the local potentials were recorded in situ, the distance between the electrodes ranging between 0.2 mm. and several millimeters. In most observations a discordance between the time-voltage-integrals (area-axis) R and T was found, the areas being either equal or unequal corresponding to a homogeneous or nonhomogeneous spread of excitation; concordance was found only rarely. It was also demonstrated that the direction of spread of excitation on the cardiac surface varied considerably over larger distances as well as smaller ones measuring only a few millimeters. In most instances the nonhomogeneities in the course of excitation showed a certain spatial orientation, namely, the action potential in the direction from base to apex increasing in velocity. These findings would tend to explain the type of ventricular gradient as found in man, namely, concordance between R and T waves in the electrocardiogram.

BRACHFELD

Kahn, M., Scheuer, J., Washtel, F., Grishman, A., and Donese, E.: An Evaluation of the Ratio of P-Wave Duration to P-R Segment in the Diagnosis of Atrial Enlargement. Am. Heart J. **60**: 23 (July), 1960.

Forty-four normal subjects, 267 patients with left, right, and combined atrial enlargement, and 25 patients with myocardial infarction were studied in regard to the ratio of P-wave duration to P-R segment. Eighty-six per cent of the normal subjects and 48 per cent of patients with atrial enlargement showed ratios between 1.0 and 1.6, the normal range in the criteria of Macruz, Perloff and Case. Only 34 per cent of the patients with right atrial enlargement had ratios below 1.0 and only 44 per cent of those with left atrial enlargement had ratios above 1.6. Combined atrial enlargement could not be diagnosed by the use of this measurement. In the patients with coronary artery disease the ratios were found to be high,

normal, and low. The authors concluded that the clinical usefulness of this ratio in diagnosing atrial enlargement was markedly limited because of inherent difficulties of measurement, the existence of falsely low or high values, the confusing results in patients with coronary disease, the frequent occurrence of normal values in the presence of atrial pathology and the apparent inability to distinguish combined atrial enlargement.

SAGALL

Maurice, P., Barrillon, A., and Lenegre, J.: Evolution of the Electric Signs of Chronic Cor Pulmonale. Arch. mal. coeur 53: 522 (May), 1960.

Of 175 patients with chronic cor pulmonale, a "P pulmonale" pattern (axis of P exceeding 60°, voltage exceeding 2.5 mm. in lead II and 2 mm. in V_1) was found in 5.5 per cent during the initial phase I, 49.4 per cent in patients with right ventricular failure (phase II), and 34.7 per cent in those where failure had disappeared (phase III). This pattern was present in three of six patients showing no right atrial hypertrophy at autopsy, in five of 10 patients showing slight hypertrophy, in nine of 15 patients showing moderate hypertrophy, and in two of three patients showing marked hypertrophy. A deviation of QRS area beyond + 110° was found in 11.1 per cent of phase I, 45 per cent of phase II, and 23.6 per cent of phase III. Inversion of the T wave in leads II and III was seen in 2.8, 48, and 25 per cent of these phases respectively while inversion of the T wave in V_2 was seen in 19.5, 52.2, and 25.8 per cent. A predominant R wave or one exceeding 10 mm. in V_1 was found only in combination with incomplete right bundle-branch block; it was found in 5.5, 25.5, and 22.2 per cent. A QRS axis exceeding + 90° with S exceeding R in V_5 and 2_R in V_6 was seen in 19.5, 42.2, and 26.3 per cent of the three phases. This compares with a mean pulmonary artery pressure of 19.6 mm. Hg in phase I, 38 mm. in phase II, and 27.7 mm. in phase III. One or more of the above signs of right ventricular hypertrophy was present in five of seven persons who had a ratio of left-to-right ventricular weight of 1.1 to 1.4 at autopsy, in 20 of 21 persons where this ratio was 0.8 to 1.1 and in all 10 persons where it was less than 0.8. In general, all these signs showed partial reversion with disappearance of right ventricular failure, but this reversion was minimal in the case of right bundle-branch block with tall R_1 waves. The incidence of this pattern also showed the greatest difference among the three groups of ventricular weight ratios.

LEPESCHKIN

Medrano, G. A., Sodi-Pallares, D., de Micheli, A., Bisteni, A., Polansky B. J. and Hertault, J.: A Study of the Potentials of the Purkinje Tissue. Am. Heart J. 60: 562 (Oct.), 1960.

The potentials of the Purkinje tissue of the dog heart were registered and charted in different regions of the interventricular septum and the free ventricular walls in 35 animals under normal conditions and after the production of complete and incomplete bundle-branch block. Experimental proof is offered to show that the deflections recorded by the technic used represented the potentials of the Purkinje tissue. With varying degrees of block a progressive delay in the inscription of these potentials was found in the blocked side when compared to the time of onset of the potentials of the bundle of His. With complete bundle-branch block delay in conduction was observed at the interventricular septum, a finding consistent with the existence of a physiologic septal barrier previously proposed by the authors.

SAGALL

Orlov, V. N.: Electrokymographic Studies of Cardiac Movement under Normal Conditions and after Myocardial Infarction. Cor et Vasa 2: 185, 1960.

Electrokymograms from a large number of points on the left ventricular border were registered synchronously with the electrocardiogram and phonocardiogram in 42 healthy controls and 45 patients with myocardial infarction scars. Phase analysis of the synchronized curves enabled differentiation of pulsatile from rotational movements. In normal persons in the frontal and first oblique positions, contraction began in most cases earlier in the apical than in the basal regions of the left ventricle; less commonly the entire left ventricular border showed simultaneous contraction that ended earlier in the basal regions. In the second oblique projection, systole always began with a dorsal rotational movement of the entire heart, followed by retraction of the cardiac contour. In the presence of a small infarction scar, outward movement of the ventricular contour was abnormal and exceeded 0.125 second or ½ of systole; in the apical region it exceeded 0.075 second. With large infarction scars a paradoxical outward movement took place during the entire systole, with retraction during diastole. A silent zone was seen only rarely. Electrokymography allowed the demonstration of anterior, posterior, and lateral infarcts in a number of patients in whom the electrocardiogram had already returned to baseline configuration at the time of the test. Simultaneous horizontal and vertical phase analy-

sis at the site of infarction enabled exact determination of the size of the postinfarction scar.

LEPESCHKIN

Pruche, A.: Importance of High Amplification in Electrocardiography. Pathologic Tracings. Arch. mal. coeur **53**: 496 (May), 1960.

Unipolar leads were registered from two roentgenologically determined precordial sites corresponding to the right and left ventricles as well as five additional sites to the left or right of these, with an amplification of 10 to 12 cm. per millivolt. This permits a more exact measurement of displacements of the S-T segment, T and U waves, and considerably reduces the percentage of patients with angina pectoris who show an apparently normal electrocardiogram. The atrial fibrillation waves registered by this method can be identified much more clearly than in conventional electrocardiography, and their frequency can be easily measured.

LEPESCHKIN

Sova, J., and Jezek, V.: Chronometry of the Cardiac Systole in Chronic Myocardial Aneurysm. Cor et Vasa **2**: 203, 1960.

The carotid pulse was registered together with the electrocardiogram and phonocardiogram in 40 patients who had shown electrocardiographic evidence of fresh myocardial infarction 1 to 3 years previously, and in 50 healthy controls. The interval between the beginning of the QRS interval and the first large vibrations of the first sound (deformation time) showed no significant differences between the two groups, but the interval between these vibrations and the beginning of the carotid pulse (isometric phase proper), as well as the sum of the two intervals (tension time) were significantly prolonged in the 20 patients in whom a ventricular aneurysm was probable on the basis of persistent S-T elevation. The average tension time in the latter was 0.1245 second as compared to a normal average of 0.097 second, while the isometric phase proper was 0.0605 second vs. 0.039 second in normal subjects. The ejection time was significantly shortened while the duration of mechanical and electric systole was prolonged in patients with aneurysm, when corrected for the heart rate. The ratio of ejection to tension time showed the greatest difference (2.08 vs. 2.93). Changes in the time relations of the cardiac cycle probably depend on systolic movement of blood into the aneurysm instead of into the aorta and are of great differential diagnostic significance.

LEPESCHKIN

Torresani, J., Nicolai, P., and Delboy, C.: Electrocardiographic Changes during Coma with Hypothermia. Arch. mal. coeur **53**: 809 (July), 1960.

A 48-year-old man, who was found on the street unconscious under the influence of alcohol on a cold winter morning, had a rectal temperature of 34.9 C. The electrocardiogram showed a wandering nodal pacemaker with a ventricular rate of 30 and a Q-T interval of 0.96 second. A slow wave 0.02 second in duration followed a slender R wave; the slow wave was upright in leads I to III and V_4 to V_6, inverted in V_1 and V_2. During rewarming this wave became short in duration and finally disappeared completely, while the initial R wave remained unchanged. At the same time the T wave, which was inverted in leads with an upright slow wave, became upright in these leads. This behavior indicated that the T-wave changes were secondary and favors the interpretation of the slow wave as being due to an intraventricular conduction disturbance rather than a "current of injury." The direction of the wave would be incompatible with right bundle-branch block, but the fact that the initial portion of the QRS complex remained unchanged would be incompatible with left bundle-branch block.

LEPESCHKIN

Unghvary, L., and Hovanyi, M.: On the Mechanism of Electric Alternation. Ztschr. Kreislaufforsch. **49**: 759 (Aug.), 1960.

After injection of epinephrine 2:1 A-V block appeared in an anesthetized dog; every second ventricular complex was characterized by a taller R wave and a smaller T wave. A monophasic action potential taken from an injured to an uninjured point on the left ventricle at the same time showed alternation between action potentials with lower amplitude, shorter duration and steeper plateau and those of normal configuration. This showed that alternation in this case was not caused by an alternating intraventricular conduction disturbance.

LEPESCHKIN

Van Bogaert, A.: Study on the Mechanism of Triple Cardiac Rhythms. Arch. mal. coeur **53**: 721 (July), 1960.

Registration of apex cardiograms and phonocardiograms in patients with atrial flutter shows that while the amplitude of the atrial waves in the cardiogram is the same throughout the ventricular cycle only waves appearing in the initial part of diastole are accompanied by audible vibrations; these waves also show a second sum-

mit that becomes lower and finally disappears toward the end of diastole. This summit, as well as the atrial sound, is attributed to vibrations of the ventricular wall caused by atrial contraction; further filling of the ventricle with blood stretches it and dampens these vibrations. These vibrations are facilitated by a reduction of myocardial tonus, either as part of a vagal effect or of myocardial failure, and the third sound or protodiastolic gallop appears under these conditions. Progression of failure may cause them to disappear because of increased residual blood; this in turn leads to atrial distention and greater force of contraction, resulting in the appearance of a presystolic gallop. In persons with a presystolic gallop the first sound and the beginning of ventricular contraction in the apex cardiogram appear later after the QRS complex than in normal subjects.

LEPESCHKIN

Zamfir, C., Turcu, E., and Teodoresco: Considerations on a Form of Wolff-Parkinson-White Syndrome of Long Duration. Arch. mal. coeur **53:** 514 (May), 1960.

An otherwise normal man started to complain of palpitation at the age of 33, at which time a typical Wolff-Parkinson-White pattern was registered in the electrocardiogram. During the next 4 years slight elevations of temperature and sedimentation rate were observed, and the pattern persisted unchanged. At the end of this time the electrocardiogram became normal and remained so, while palpitation persisted. The course of the disease favored the interpretation that it was caused by a temporary organic process near the atrioventricular node that led to increased irritability there, and emphasizes the variability in the pathogenesis of the syndrome.

LEPESCHKIN

Zuckermann, R.: Right Bundle Branch Block with Right Ventricular Hypertrophy. Ztschr. Kreislaufforsch. **49:** 811 (Sept.), 1960.

A patient with marked right ventricular hypertrophy as part of Fallot's tetralogy showed marked right axis deviation and a tall R wave in V_1. After operative correction of the malformation, right bundle-branch block appeared; this did not change the initial 0.04 second of the QRS complex but caused a slow terminal portion of QRS to appear, which was positive and of high voltage in V_1 and negative in V_5 and V_6. Right bundle-branch block accompanying hypertrophy of the entire right ventricle including the septum was characterized by tall R and R′ waves in V_1. If hypertrophy was confined largely to the lateral wall of the right ventricle, V_1 should show an M-shaped QRS complex with a low initial and high terminal summit, and the appearance of right bundle-branch block in this instance should lead to high voltage only of the wide R′ wave but not of the R wave.

LEPESCHKIN

HYPERTENSION

Berliner, K., Fujiy, H., Lee, D., Yildiz, M., and Garnier, B.: The Accuracy of Blood Pressure Determinations. A Comparison of Direct and Indirect Measurements. Cardiologia **37:** 118, 1960.

Direct intra-arterial blood pressure measurements by means of an electromanometer and indirect blood pressure determinations with the auscultatory method were made simultaneously in 100 patients. The indirect method underestimated systolic blood pressure in 61 per cent of patients and overestimated diastolic pressure in 63 per cent of patients. The discrepancies were minor (less than 10 mm. Hg) in most instances. Gross discrepancies can usually be avoided by painstaking technic, especially in using the auscultatory method. It was concluded that the auscultatory method of blood pressure determination, if practiced carefully, is a reliable clinical method.

BRACHFELD

Dickinson, C. J., and Thomson, A. D.: High Blood-pressure and Stroke. Lancet **2:** 342 (Aug. 13), 1960.

Narrowing of the vertebral artery has been shown to be more closely associated with high blood pressure than narrowing of the internal carotid artery. Moreover, in people dying of strokes, the volume of the main cerebral arteries is reduced with no difference between cerebral hemorrhage and cerebral softening or infarction. It was postulated that strokes in the vertebral artery territory should be associated with slightly higher blood pressures than those in the internal carotid territory and that high blood pressure should be as closely associated with cerebral softening infarction as it is with cerebral hemorrhage. These two predictions were tested by a retrospective necropsy study of 340 cases of cerebrovascular lesions or strokes in which there was no evidence of precipitating cause other than high blood pressure or arterial degeneration. Two main conclusions could be drawn. The first is that the heart weight is probably greater in people with hind-brain as opposed to fore-brain strokes. The second is the difficulty in demon-

strating any difference between the hearts of people with cerebral hemorrhage and cerebral infarction. These results support the opinion that narrowing of the main cerebral arteries has a causal role in benign essential hypertension and that cerebral hemorrhage and cerebral infarction both have the same cause.

KURLAND

Dollery, C. T., Emslie-Smith, D., and Milne, M. D.: Clinical and Pharmacological Studies with Guanethidine in the Treatment of Hypertension. Lancet **2:** 381 (Aug. 20), 1960.

Eighty patients who had severe hypertensive disease were treated with guanethidine over a period of 9 months. Over half had had retinal hemorrhages, and three-quarters were admitted to the hospital for stabilization. Since the pressure-lowering action of guanethidine is a result of a blockade of the sympathetic vasomotor system and the fall in pressure is greatest when the patient is upright, the aim was to achieve normal or nearly normal pressures in the standing position. Doses ranged from 10 to 750 mg. daily, but most patients received between 30 and 120 mg. Since guanethidine has a cumulative action, 3 days were allowed between alterations of dose so that a steady effect was reached. Thirty-four of the 80 patients experienced good control of blood pressure, standing blood pressure 160/100 mm. Hg or lower. Thirty-four had fair control of blood pressure with reduction of diastolic by at least 20 mm. Hg. There were eight patients in whom treatment was regarded as a failure, two because of drug resistance, two because of tremor, and two because of depression. The reduction of blood pressure was greatest when the patient first rose from bed and often produced symptoms at this time. A fall in blood pressure on effort was noted and not confined to effort in the standing position. A variety of side effects was noted, but their incidence and severity were much less than with the ganglionic blocking agents and comparable to the incidence found with Bretylium. Most patients passed only semiformed stools and a number had frank diarrhea. Bradycardia was noted in many. Carotid tenderness and nasal obstruction were noted. Six patients developed a coarse muscle tremor. Weight gain and edema were noted and four patients developed a clinical picture of congestive heart failure. Five patients complained of dyspnea on exertion that occurred when pressure control was good and there were no signs of heart failure. Weakness, tiredness, and depression were common. Failure of ejaculation was noted in some male patients. There has been no evidence of progressive increase of dose requiremnt. Intravenous doses were given to 14 patients, and a rapid fall in blood pressure was noted which appeared quite satisfactory for urgent reduction of pressure. When labeled guanethidine was given by mouth to patients, 36 per cent was recovered from the urine in 72 hours. When it was injected intravenously, the recovery was 72 per cent in the same time. Recovery of orally administered guanethidine from the feces was 20 to 25 per cent. Distribution of guanethidine in the organs of rats was predominantly intracellular and the plasma concentration was low. The highest concentrations of guanethidine were found in the kidney. It is excreted in the urine unchanged and as 3 closely related metabolites.

KURLAND

Dykman, R. A., and Gantt, W. H.: Experimental Psychogenic Hypertension: Blood Pressure Changes Conditioned to Painful Stimuli (Schizokinesis). Bull. Johns Hopkins Hosp. **107:** 72 (Aug.), 1960.

Blood pressures were measured in dogs by a modified cuff method and conditioning was produced to signals associated with reinforcing unconditioned stimuli. In the first group of dogs the conditioning had been terminated 13 months previously after a year of training; these animals exhibited 3 conditioned reflexes of graded intensities with differentiated motor, cardiac, and blood pressure components that were directly proportional in magnitude to the 3 intensities of unconditional stimuli. Thus blood pressure could be conditioned in dogs not only qualitatively to excitatory and inhibitory signals, but, specifically, to the quantitative significance of the signal. The conditioned hypertension was retained for a 13-month rest period without intervening training and was present immediately when the dog was brought back into the environment where the stress had been given; the authors speculate that this may be equivalent to chronic hypertension. In addition, they note that hypertension may be experimentally produced by psychogenic stress.

KARPMAN

Evanson, J. M., and Sears, H. T. N.: Comparison of Bretylium Tosylate with Guanethidine in the Treatment of Severe Hypertension. Lancet **2:** 387 (Aug. 20), 1960.

The action of bretylium tosylate and guanethidine were compared in 44 cases, 29 of whom were judged to have malignant hypertension from the level of a diastolic blood pressure and the presence of papilledema; the remaining 15 all had severe benign hypertension with diastolic

pressures of over 120 mm. Twenty-seven patients received bretylium and 17 guanethidine. Bretylium tosylate was started at a dose of 200 mg. three times daily. Guanethidine was begun with 10-mg. daily doses, but later 20-mg. doses were used. Initial hospital stabilization was followed by outpatient supervision. The goal of therapy was a standing diastolic pressure of approximately 100 mm. Hg. The response to treatment in each patient was evaluated in terms of the fall in blood pressure, improvement in symptoms, change in retinal appearances, and the patient's general condition. Patients who had been discharged from the hospital on bretylium tosylate showing a good response to the dose given at that time, were almost always found to have uncontrolled hypertension when they made their first outpatient attendance. Subsequent attempts at outpatient control proved time-consuming and difficult. In contrast to this, it was unusual for patients on guanethidine to require more than minor adjustment in dosage in the clinic, and half of them needed no change from the hospital regimen. Side effects of bretylium treatment included nasal stuffiness, dyspnea, severe parotid pain, diarrhea, and muscular weakness. With guanethidine, diarrhea was the most troublesome feature, but mild exertional dyspnea was also noted. Mental changes were observed with both drugs. The authors conclude that at present guanethidine is the drug of choice. Its action appeared steady, tolerance did not develop, and outpatient care was relatively easy.

KURLAND

Hobolth, N.: Hypotensive Action of Hydroflumethiazide. Acta med. scandinav. **168**: 71, 1960.

Eighteen hypertensive patients completed a study on the efficacy of hydroflumethiazide alone or combined with reserpine or pentamethylpiperidine. Some patients who had previously been on ganglion-blocking agents could be managed without these. Five patients did not benefit from the addition of hydroflumethiazide. The author recommended a prophylactic supplement of potassium chloride to prevent hypokalemia. The serum sodium did not fluctuate beyond the normal range, there was no change in blood urea or serum creatinine level, but frequently there was an increase in total carbon dioxide (exceeding the upper limit of normal in 12 of the 18 patients). In a few patients the potassium chloride supplement was increased to 6 Gm. daily (above the usual dose of 3 Gm. daily) to avoid hypokalemia. No symptomatic side effects were noted.

SHEPS

METABOLIC EFFECTS ON CIRCULATION

Gallo, P.: Biochemical Significance of Myocardial Tissue Changes Associated with Rigor Mortis, under Normal Conditions and in Experimental Poisoning with Gamma-Hexane. Cardiologia, Suppl. I, **37**: 3, 1960.

Histologic studies showed that adenosinetriphosphate and phosphocreatine are not uniformly disturbed throughout the myocardial tissue: in some areas (approximately 20 μ in diameter) the concentration level of such substances was lower than in the remainder of the tissue. Also, the rate of chemical energy production was not uniform, being lower in areas with a lesser adenosinetriphosphate content. It was tentatively suggested that these findings may be due to the fact that in the aforementioned areas the yield of oxidative phosphorylation processes is smaller than in the rest of the tissue. In the rabbit, topical application of gamma-hexane on the skin, 2 mg./Kg. twice weekly, did not alter the course of myocardial tissue changes associated with rigor mortis, which exhibited a pattern almost identical to that observed in animals not treated with this insecticide.

BRACHFELD

Gonin, A., Berger, M., Mornex, R., Grandmottet, P., and Pelloux H.: Therapeutic Effects of Radioactive Iodine in Cardiac and Coronary Insufficiency. Arch. mal. coeur **53**: 537 (May), 1960.

Twenty-six cardiac patients were treated with an initial dose of 15 millicuries of radioactive iodine, further treatment depending on the effect on the protein-bound iodine; the total dose did not exceed 45 millicuries in 6 months. A dose of less than 15 millicuries was ineffective. Among three patients with intractable congestive failure two died without improvement, in spite of development of marked myxedema; while in one, improvement was slight. Of nine patients with intractable angina pectoris, six showed good or excellent results, which appeared without the patient knowing when to expect them and without any improvement in the electrocardiogram; one patient died of acute coronary thrombosis after signs of thyroiditis had developed. Of 14 patients with decompensated aortic stenosis, one responded to treatment, six showed excellent improvement in dyspnea, anginal complaints, and working capacity, but no improvement in the electrocardiogram. Four patients died, one as a result of marked myxedema after temporary improvement. These patients all had been decompensated more than 2 years. As these patients

are beyond surgical treatment, a trial with radioactive iodine seems to be justified in them.

LEPESCHKIN

Nayler, W. G.: Effect of Strophanthin G on Oxidative Metabolism in Cardiac Muscle. Nature **188:** 70 (Oct. 1), 1960.

Strophanthin G stimulates oxidative metabolism in actively beating hearts but fails to do so in hearts that have been arrested in either systole (with calcium chloride) or diastole (with potassium chloride). These results may be explained by the effect of the glycoside on a specific stage during contraction or relaxation or, alternatively, the effect may be primarily due to raised work output associated with a positive inatropic response in the actively beating heart. It seemed unlikely to the author that a gross metabolic effect could be involved.

SHEPS

PATHOLOGY

de la Cruz, M., Anselmi, G., Romero, A., and Monroy, G.: A Qualitative and Quantitative Study of the Ventricles and Great Vessels of Normal Children. Am. Heart J. **60:** 675 (Nov.), 1960.

One hundred normal unfixed hearts from autopsies of children ranging in age from 6 months of intrauterine life to 12 years were examined in regard to certain anatomic features. The thickness of the walls of both ventricles increased with age. The thickness of the left ventricle increased markedly with age, being most marked in the lateral position. Only slight increase in thickening was found with age in the right ventricle, and the anterior border remained the thinnest portion. In general, in all the hearts studied, including those of premature and newborn infants, the wall of the left ventricle was thicker than that of the right and the mean thickness of the left ventricle was more than double that of the right ventricle. Study of the ventricular outflow tracts indicated that the outflow tract of the right ventricle was the largest and grew the most, whereas the inflow tract of the right ventricle not only was the smallest tract but grew the least. With age there was an increase in the circumference of the orifices of the great vessels, the circumference of the trunk of the pulmonary artery, the circumference of the ascending portion of the arch of the aorta, the length of the trunk of the pulmonary artery, and the length of the infundibulum of the pulmonary artery. The circumference and area of the tricuspid orifice were found to be greater than those of the mitral orifice. The diameter and the circumference of the orifice of the pulmonary artery and of the pulmonary artery itself were greater than those of the aorta. The annulus of the valve of the pulmonary artery increased proportionately in relation to the inferior circumference of the infundibulum.

SAGALL

Kisch, B.: On Nerve Terminations in Ventricular Muscle. Ztschr. Kreislaufforsch. **49:** 762 (Aug.), 1960.

Electron microscopic studies on animals as well as one human specimen obtained by needle biopsy immediately after death showed that ventricular muscle contains terminations of autonomic nerves. These terminations of proto-axons have intimate contact with the sarcolemma of the muscle fibers. The number of terminations in muscle fibers is considerably smaller than that in the capillaries surrounding them.

LEPESCHKIN

Obrucník, M., and Kotrle, M.: Studies with Fluorescence Microscopy on the Intima of Human Coronary Arteries. Cor et Vasa **2:** 174, 1960.

Primary as well as secondary fluorescence caused by phosphine 3R, aurophosphine, auramine, acridine orange, methylene blue, and pyronine in high dilution and at varying pH provides more exact localization of lipids than corresponding histochemical methods. Study of 15 normal hearts and 15 hearts with severe atherosclerosis with these methods showed that lipids are accumulated predominantly in the anterior descending branch and at the origin of both coronary arteries. The earliest changes consist of accumulation of fibrocytes with lipoid granules in the subendothelial zone of the intima. The fibrocytes swell and finally disintegrate, losing their granules into the interstitial substance, where they may coalesce into clumps and become surrounded with fibrous tissue. The earliest deposits consist of neutral fats, lipoproteins, fatty acids, and glycolipids; cholesterol appears only in advanced phases.

LEPESCHKIN

Sutton, D. D., and Sutton, G. C.: Needle Biopsy of the Human Ventricular Myocardium: Review of 54 Consecutive Cases. Am. Heart J. **60:** 364 (Sept.), 1960.

One hundred and fifty needle myocardial biopsies were obtained in 54 patients during pericardiotomy, thoracotomy, and cardiac surgery and, most commonly, by the percutaneous route. There was no mortality or serious morbidity. The most common, but not invariable, reaction

was that of scattered ectopic ventricular beats or short runs of ventricular tachycardia. No serious bleeding was encountered. The specimens obtained by this method were satisfactory for the microscopic detection of normal myocardium, myofibrosis, diffuse myocarditis, fibroelastosis, collagen disorders, and lipomatosis. Three cases illustrating the value of this procedure are presented.

SAGALL

PHARMACOLOGY

Conn, H. L., Jr., and Wood, J. C.: Acute Effects of Quinidine on K Exchange and Distribution in the Dog Ventricle. Am. J. Physiol. **199**: 151 (July), 1960.

Some effects of quinidine in therapeutic or low-toxic concentrations on radiopotassium kinetics and gas exchange were observed in the isolated perfused dog heart. Oxygen consumption and the respiratory quotient decreased and cellular potassium increased; this occurred chiefly during the initial resting phase, and there was little or no potassium flux during the action potential.

ROGERS

Ellis, C. H.: Antagonism of Drug-Induced Pulsus Alternans in Dogs. Am. J. Physiol. **199**: 167 (July), 1960.

Pulsus alternans was induced in anesthetized dogs by the intravenous injection of a hypertensive drug, usually methoxamine 0.4 to 1.0 mg. per Kg. It was decreased or abolished by administering digoxin, oubain, norepinephrine, theophylline, histamine, nitroglycerin, hexamethonium, quinidine, o-methylcyclizine, a new antiarrhythmic agent (B.W. 51-41), by stellate ganglion stimulation, or by hemorrhage. Administration of procaine amide was ineffective. While the mechanisms responsible for the development of pulsus alternans were not clear, it appeared that it could be antagonized by agents possessing a positive inotropic action, by those reducing peripheral arterial resistance, and by some of those that were antiarrhythmic.

ROGERS

Farrelly, R. O., Howie, R. N., and North, J. D. K.: Use of Spironolactone and Hydrochlorothiazide in Treatment of Oedema. Brit. M. J. **2**: 339 (July 30), 1960.

In recent years the role of excessive aldosterone secretion in the genesis and maintenance of edema, whether due to cirrhosis with ascites, congestive failure, or the nephrotic syndrome, has been recognized and efforts have been directed toward the development of aldosterone antagonists. The purpose of this study was to evaluate the clinical effectiveness of spironolactone, a new aldosterone antagonist. Aldosterone secretion is low in normal individuals on a high-sodium intake as well as in edematous patients who are in a "steady state" and not actively retaining sodium. Thus, spironolactone has little diuretic effect on this type of patient. The study was carried out on seven patients (five with congestive heart failure and two with the nephrotic syndrome) for a 16-day period divided into units of 4 days each with a schedule as follows: The first period consisted of diet and bed rest alone. Diet was constant with sodium 22 mEq./day, potassium 78 or 65 mEq./day, and fluid 1,600 ml./day. In the second period—diet plus hydrochlorothiazide, 200 mg. daily in 6-hour doses was added. In the third period spironolactone, 800 mg. daily in 6-hour doses was included. The fourth period was the same as the second. A daily record of weight, blood pressure, urine volume, and degree of edema was obtained. Sodium excretion was increased significantly in six of the seven patients when spironolactone was given along with hydrochlorothiazide; potassium excretion was decreased in all patients; the administration of spironolactone to patients with the nephrotic syndrome did not alter the rate of weight loss and in only one patient was there an increase in sodium excretion with a decrease in potassium excretion. The authors believe that administration of spironolactone is of limited value in the treatment of cases of refractory edema but that it will definitely protect the patient against hypokalemia associated with the use of hydrochlorothiazide.

KRAUSE

Fleisher, R. R., and Linde, L. M.: Gitalin Studies. Am. Heart J. **60**: 520 (Oct.), 1960.

Since Batterman in 1950 published evidence to show that the therapeutic ratio of gitalin was significantly less than that of other digitalis preparations, the drug has been studied extensively. Variable conclusions as to its therapeutic value have been reported. In 1956, Haack and co-workers discovered that gitalin was a glycosidal mixture that contained two new glycosides, gitaloxin and formyl-strospeside, potent and extremely labile constituents whose presence was not considered in the previous research on the drug. On the basis of this advance in the chemical knowledge of gitalin, re-evaluation of the previously reported conflicting results and new investigations are indicated. The author further points out that biologically inactive leaf substances, which make up about half of the "gitalin fraction," have been found to increase the solu-

bility and diffusability of cardiac glycosides. He also suggests standards for future clinical trials of cardiac glycosides.

SAGALL

Kohli, J. D., and Vohra, M. M.: Pharmacological Studies on Peruvoside—A New Cardiac Glycoside from Thevetia neriifolia Juss. Arch. int. pharmacodyn. **126:** 413 (July), 1960.

Thevetia neriifolia Juss produces positive inotropic effect on hypodynamic heart. On perfusion into cats, it produces electrocardiographic changes typical of a cardiac glycoside. It produces emesis in pigeons and has musculotropic activity on other smooth muscles. It is a highly active glycoside with lethal dose of 147.4 μg./Kg. ± 6.6 in cats, 709.9 μg./Kg. ± 58.9 in guinea pigs, and 203.2 μg./Kg. ± 22.7 in pigeons. Peruvoside is quickly and well absorbed from the gastrointestinal tract. It has a very short lag period between administration and cardiac activity. The duration of action is rather short and cumulative toxicity low.

BRACHFELD

Lasser, R. P., Schoenfeld, M. R., and Friedberg, C. K.: L-Lysine Monohydrochloride: A Clinical Study of Its Action as a Chloruretic Acidifying Adjuvant to Mercurial Diuretics. New England J. Med. **263:** 728 (Oct. 13), 1960.

In 20 patients suffering from fluid retention due to cardiac or liver disease, L-lysine monohydrochloride in doses of 10 to 40 Gm. daily was found to be a satisfactory chloruretic and acidifying agent. Vigorous acidification with this drug (40 Gm. daily for 3 days) prior to the administration of a mercurial diuretic often restored responsiveness in those patients previously refractory to the mercurials. In cold fruit juice or low-sodium milk the drug was well tolerated. The only side effects noted consisted of abdominal cramps and transient diarrhea disappearing with reduction of dosage. With L-lysine monohydrochloride ammonia intoxication was not encountered in the patients with liver dysfunction.

SAGALL

Lee, Y. C.: Quinidine Intoxication: An Experimental Study of the Effect of Molar Sodium Lactate and Potassium Chloride. Am. Heart J. **60:** 785 (Nov.), 1960.

Observations were made in anesthetized dogs following the intravenous administration of quinidine and the prior or subsequent infusion of molar sodium lactate and potassium chloride. After the intravenous administration of quinidine there was a definite decrease in the concentration of plasma potassium and in the arterial blood pH, but no significant change in plasma sodium. When quinidine was followed by molar sodium lactate, there was noted a further decrease in plasma potassium, a moderate increase in blood pressure and pulse rate, a narrowing of the P-R interval and the QRS duration, and the development of prominent U waves. Prophylactically administered molar sodium lactate did not prevent the hypotensive effect of quinidine and showed no significant beneficial effect on severe quinidine intoxication. The effect of quinidine was not enhanced by the prior administration of potassium chloride, but in two of five dogs given potassium chloride after quinidine a significant increase in pulse rate and blood pressure was observed. The possible mechanisms of action of molar sodium lactate are discussed. The question as to whether molar sodium lactate has any place in the treatment of quinidine intoxication still has to be determined.

SAGALL

Schoolman, H. M., Bernstein, L. M., Littman, A., and Pascale, L. R.: Acetylcholine in Differential Diagnosis and Treatment of Paroxysmal Tachycardia. Am. Heart J. **60:** 526 (Oct.), 1960.

Data are presented to illustrate the diagnostic and therapeutic value of acetylcholine in paroxysmal tachycardia. Acetylcholine, from 20 to 80 mg. administered intravenously, terminated paroxysmal nodal tachycardia in seven of nine patients, and paroxysmal atrial tachycardia in one of two patients. Of these 11 patients eight were thus successfully treated with acetylcholine without recurrence. In 14 patients with atrial flutter and rapid ventricular rate, acetylcholine terminated the rhythm in only two patients, and in both there was recurrence. In two patients with paroxysmal ventricular tachycardia acetylcholine in doses up to 200 mg. was without effect. In eight patients with normal duration of the QRS complex and in whom atrial flutter was suspected, acetylcholine caused transient A-V block, thereby clearly revealing the flutter waves and helping to establish the diagnosis. In another patient the acetylcholine induced transient A-V block, established the diagnosis of atrial tachycardia with 1:1 A-V conduction rather than nodal tachycardia, which had been diagnosed previously. In six patients with atrial flutter and bundle-branch block simulating ventricular tachycardia, the transient A-V block induced by acetylcholine allowed unequivocal measurement of flutter waves between ventricular complexes, thus clearly indicating the true mechanism of the arrhythmia. Side reactions to acetylcholine in the manner administered were mild, transient, and not clinically significant.

SAGALL

Weiss, W. A.: Intravenous Use of Lidocaine for Ventricular Arrhythmias. Current Res. Anesth. & Analg. 39: 369 (July/Aug.), 1960.

A total of 363 patients undergoing cardiac surgery received 2 per cent lidocaine (Xylocaine) in an average intravenous dosage of 1 mg. per Kg. of body weight. This was given prophylactically 47 times; the therapeutic indications included frequent ventricular premature systoles, especially if appearing in bigeminal rhythm, ventricular tachycardia, and ventricular fibrillation. Within 35 to 90 seconds after injection a decrease in ventricular irritability was usually observed; the duration of this effect was approximately 10 minutes. The drug could be repeated every 10 minutes for a maximum of four administrations without toxic manifestations. A favorable response was obtained in 87.3 per cent of patients. Injection of a 1 per cent solution was not as effective while an intravenous drip of a 0.1 to 0.2 per cent solution usually caused only widening of the QRS complex without a commensurate decrease in ventricular irritability.

LEPESCHKIN

PHYSICAL SIGNS

Breen, W. J., and Rekate, A. C.: Effect of Posture on Splitting of the Second Heart Sound. J. A. M. A. 173: 1326 (July 23), 1960.

Splitting of the second heart sound is of value in the diagnosis of certain congenital and acquired heart diseases as well as in certain conduction disturbances. It is important to distinguish physiologic from pathologic splitting of this sound. If splitting of the second sound disappears with expiration, it is called physiologic. This change can be noted by auscultation. The persistently split second heart sound with the patient in the supine position may be normal or may indicate cardiac disease. In some cases, splitting may disappear when the patient changes his position from supine to upright. This postural change in the second heart sound separates persons with a normal variant from those in whom splitting is a sign of cardiac disease.

KITCHELL

Comisioneru, N.: The Sign of the Porto-Spleno-Inferocaval External Jugular Venous Reflux. Arch. mal. coeur 53: 556 (May), 1960.

Manual pressure on the liver, spleen, or the inferior vena cava in the umbilical region, in the recumbent patient, causes swelling of the external jugular vein as an early and constant sign of right ventricular and atrial failure. In order to demonstrate this sign clearly, it is necessary to position the patient's head properly and to instruct him to keep the sternocleidomastoid muscles relaxed. The value of this sign is illustrated with case histories of 19 patients.

LEPESCHKIN

PHYSIOLOGY

Bevegard, S., Holmgren, A., and Jonsson, B.: The Effect of Body Position on the Circulation at Rest and during Exercise with Special Reference to the Influence on the Stroke Volume. Acta. physiol. scandinav. 49: 279, 1960.

Studies were made on the same subject in regard to the behavior of stroke volume at rest and during exercise. Ten healthly male subjects were studied by means of right heart and brachial artery catheterizations. Cardiac output was determined by the direct Fick principle. No significant difference was noted in pulse rate either in the supine or sitting position before or after catheterization. Before exercise, with change from supine to sitting position, there was increased arteriovenous oxygen difference, the cardiac output decreased, the pulse rate increased, and the stroke volume decreased on the average about 40 per cent. With change from the supine to the sitting position there was a shift of blood from the thorax to the legs with decrease of heart volume and with consequent impaired diastolic filling a decrease in stroke volume. During exercise in the supine position arteriovenous oxygen difference and cardiac output increased with increasing work intensities. Stroke volume remained fairly constant. In the sitting position arteriovenous oxygen difference was higher and the cardiac output lower than in the supine position. The stroke volume increased greatly during the transition from rest to mild work. It continued to increase with increase in work but to a lesser degree with the greater amounts of work. Even at the highest load it was lower than in the supine position. However, the work performed at a pulse rate of 170 beats per minute was the same in the supine and sitting positions. This is explained by a better utilization of the oxygen in the sitting position giving an oxygen pulse (oxygen transport per beat) of the same size as in the supine position.

LEVINSON

Borgstrom, K., Ising, U., Linder, E., and Lunderquist, A.: Experimental Pulmonary Edema. Acta radiol. 54: 97 (Aug.), 1960.

Three experiments were performed to produce pulmonary edema in 16 mongrel dogs; in the first experiment, increased permeability of the bron-

chial capillaries was produced by the injection of sodium desoxycholate (SDO) into the right sixth or fifth intercostal artery; in the second experiment, SDO was injected through a catheter positioned in the pulmonary artery; in the third experiment, the ureters were ligated, physiologic saline was administered, and a balloon catheter was inflated to occlude the descending aorta; all three experiments resulted in pulmonary edema. The bronchial capillary edema was characterized by edema, especially marked in the hilar regions and a heart of normal size; pulmonary capillary edema was not confined to the hilar area but extended all the way to the periphery, with a normal cardiac silhouette. The left heart failure edema was manifested by increasing intensity toward the periphery, negligible central changes, the early appearance of cardiomegaly, and roentgenologic signs of lung changes preceding the clinical picture of pulmonary edema by 1½ hours. Only slight and temporary elevation of the pulmonary wedge pressure was produced by the infusion of physiologic saline solution in an amount equal to 10 per cent of the body weight.

KALMANSOHN

Brachfeld, N., Monroe, R. G., and Gorlin, R.: Effect of Pericoronary Denervation on Coronary Hemodynamics. Am. J. Physiol. **199:** 174 (July), 1960.

Meticulous stripping of the adventitia and the more superficial tissue from the roots of the aorta and pulmonary artery and from the principal coronary arteries with application of a 25 per cent phenol solution was followed in 10 of 12 dogs by an increase in coronary blood flow and a decrease in oxygen extraction. Phenolization alone was relatively ineffective. It was concluded that the coronary autonomic nerves maintained a degree of vasoconstriction which was abolished when the nerves were destroyed.

ROGERS

Guz, A., Kurland, G. S., and Freedberg, A. S.: Relation of Coronary Flow to Oxygen Supply. Am. J. Physiol. **199:** 179 (July), 1960.

The coronary arteries of the isolated rabbit heart were perfused with Ringer-Locke solution containing various amounts of bovine hemoglobin in equilibrium with 3 per cent carbon dioxide and 97 per cent air. The perfusates were identical in electrolyte concentration and oxygen saturation while oxygen content varied from 2 to 18 volumes per cent. A constant pressure of 60 cm. of water was used. In all of 12 experiments, reduction of perfusate hemoglobin concentration was followed immediately by an increase in coronary flow rate; and increased hemoglobin concentrations led to decreased coronary flow, the magnitude of which was unpredictable. The heart rate, left ventricular tension generated per beat, and oxygen consumption remained constant provided the perfusate oxygen capacity did not fall below 2 volumes per cent. It was suspected that the coronary flow alterations may have resulted from the elaboration or suppression of a vasodilator metabolite with or without an axon reflex.

ROGERS

Halliday, M. A.: Blood Flow in the Human Calf after Prolonged Walking. Am. Heart J. **60:** 110 (July), 1960.

By venous occlusion plethysmography blood flow in the calf of three normal male subjects was measured before and after natural walking of distances of 0.4 to 3.2 Km. at speeds of 4.8 Km./hr. and 8.04 Km./hr. It was found for each distance walked that the hyperemia after walking at 8.04 Km./hr. was greater than that after 4.8 Km./hr.; that the hyperemia increased with distance at 8.04 Km./hr., but at 4.8 Km./hr. the effect of distance was slight; and that the relationship between severity of exercise and postexercise hyperemia was not a rigid one. It was concluded that when a subject walks at 4.8 Km./hr., the blood flow requirements of his muscles are met satisfactorily by the blood vessels of the calf during the period of exercise, but that when the speed of walking increases to 8.04 Km./hr. these blood vessels are less able to satisfy the demand and a greater postexercise hyperemia is needed as the walking distance increases.

SAGALL

Hohnen, H. W., and Meese, Th.: On the Influence of Nitroglycerine on Stroke and Minute Volume of the Heart. Ztschr. Kreislaufforsch. **49:** 640 (July), 1960.

A sublingual dose of 0.8 mg. of nitroglycerin caused in 12 normal persons an increase of the ventricular stroke volume, determined from the ultralow-frequency ballistocardiogram of Klensch, while heart rate and blood pressure showed no significant changes. The multiple-slit roentgenkymogram showed increased amplitude of pulsation and decreased diastolic cardiac volume. The increase in pulsation amplitude showed a linear relation to the increase in stroke volume. In this case the relation between cardiac diastolic volume and stroke volume was opposite to that required by Starling's law.

LEPESCHKIN

Johnson, P. C., and Sevelius, G.: Measurement of Myocardial Blood Flow. J. A. M. A. 173: 1231 (July 16), 1960.

By means of a new radioisotope technic for the simultaneous measurement of coronary blood flow and cardiac output, a comparison in terms of increased myocardial blood flow is made between sublingually given nitroglycerin and orally given pentaerythritol tetranitrate (PETN) in individual patients. Myocardial blood flow and cardiac output were determined by radioisotope methods in each patient before and after the administration of the drugs. This was done by monitoring with a scintillation detector on the chest wall the first passage of a radioactive bolus through the right and left sides of the heart and through the myocardial circulation. A time activity curve was obtained and it was possible to determine both myocardial blood flow and cardiac output from this. Radioiodinated human serum albumin was used as the tracer substance to determine cardiac output and in other curves radioactive iodopyracet was used as the tracer substance. The authors found that 10 minutes after the sublingual administration of 0.6 mg. of nitroglycerin there was an increase in myocardial blood flow without change in the cardiac output in patients with arteriosclerotic heart disease. PETN produced a prolonged increase in myocardial blood flow beginning within 1 hour after ingestion and lasting up to 5 hours without changing the cardiac output in patients with arteriosclerotic heart disease and previous infarction.

KITCHELL

Levowitz, B. S., Ford, W. B., and Smith, J. W., Jr.: The Use of Direct Stimulating Myocardial Electrodes in Complete Atrioventricular Block. J. Thoracic Surg. 40: 283 (Sept.), 1960.

A bipolar myocardial electrode was implanted directly by thoracotomy in three patients with acquired atrioventricular block associated with Stokes-Adams seizures. All of these had failed to respond to medical management in conjunction with an external pacemaker over a long period. Two types of cases were noted in which this procedure was thought to be indicated. In one group there was a chronic state of circulatory insufficiency attended by frequent syncopal and convulsive paroxysms. In another group were patients with third-degree heart block, who, over a period of months or years, demonstrated progressive ventricular slowing to rates ranging between 20 to 40 per minute. The latter group was difficult to control with an external pacemaker. Two of the three patients had done well over a period of 7 months. Infection introduced through the transthoracic cable has been a problem and has been refractory to treatment. It was responsible for the death of one of these patients. Sixth molar sodium lactate and sympathomimetic amines were valuable in the immediate postoperative period to combat hypotension and the apparent refractoriness of the ventricular myocardium to the imposed impulse.

LEVINSON

Lutembacher, R.: Calcium and Myocardial Plasticity. Arch. mal. coeur 53: 490 (May), 1960.

In moderate concentrations (1:200 to 1:150) calcium chloride reduces the elongation of the frog ventricle caused by loading it with a given weight, and reduces also the residual elongation after withdrawal of the weight. Due to reduced diastolic relaxation, the amplitude of systolic contraction decreases. The duration of mechanical systole increases, while that of electric systole decreases considerably. The heart rate decreases, and ventricular extrasystoles appear singly and in runs. During the latter the ventricle does not relax, remaining contracted for 6 to 7 seconds at a time.

LEPESCHKIN

Read, R. C., Johnson, J. A., Vick, J. A., and Meyer, M. W.: Vascular Effects of Hypertonic Solutions. Circulation Research 8: 538 (May), 1960.

Concentrated alkalies administered intra-arterially were found to cause a decrease in the arteriovenous pressure difference at a constant flow. Hypertonic solutions of glucose and sodium chloride likewise decreased peripheral resistance. Hyperosmotic solutions then were injected rapidly by vein into the intact and vagotomized dog. It was found that when concentrations up to 1,500 milliosmols per liter were used the predominant response was delayed hypotension consistent with peripheral vasodilatation. When solutions containing more than 2,000 milliosmols per liter were administered, however, this reaction was preceded by transitory pulmonary hypertension. This acute pulmonary hypertension was severe after the injection of 20 per cent solution of sodium chloride, and these animals frequently died from acute cor pulmonale. Studies in the isolated perfused lung revealed that all solutions with an osmolarity equal to or greater than a 5 per cent solution of sodium chloride are able to produce pulmonary hypertension. The only exceptions to this were solutions of urea. The hypotensive response in the pulmonary vascular bed could not be brought about when the perfusing solution was free of red cells. Microscopic examination of sections from various organs disclosed that intravascular

red-cell agglutination did occur after intra-arterial injections of highly concentrated solutions. It was postulated that alterations in the stability of the red cell stream were responsible for the obstructive effects of hyperosmotic agents, previously attributed to vasospasm.

SCHIRGER

Roszkowski, A. P., and Koelle, G. B.: Enhancement of Inhibitory and Excitatory Effects of Catecholamines. J. Pharmacol. & Exper. Therap. **128:** 227 (Mar.), 1960.

Enhancement of both excitatory and inhibitory responses to epinephrine, *l*-norepinephrine, and Isoproterenol was demonstrated with cocaine, ephedrin, 2-amino-4-(diethyl-aminoethylamino)-6, 7-diphenylpteridine-(McN537), and 1-2-amino-3, 4-dimethyl-5-phenyl-thiazolidine hydrochloride (McN-X-190). Excitatory responses studied included blood pressure and contraction of the nictitating membrane of the cat; the inhibitory responses were blood pressure and uterine relaxation in the cat, and bronchodilatation in the dog. None of the four compounds produced enhancement of the inhibitory effects of the catecholamines on the isolated guinea pig tracheal chain or rabbit ileum. Of the possible mechanisms involved in producing the observed enhancement of the effects of the catecholamines in situ, the authors suggest that these drugs may interfere with physical processes, such as passage through cellular membranes or adsorption to constituents of the blood or tissues, and adrenergic blockade. These mechanisms are probably of more importance than enzymatic degradation, especially when relatively small amounts of the catecholamines are involved. Thus, at least two opposing factors may be involved: potentiation and adrenergic blockade. Depending upon drug dosage and certain other factors, the effects of the catecholamines could be increased, unchanged, or decreased.

SHEPS

Schenk, W. G., Jr.: Methods for Measurement of Blood Flow. Surg., Gynec. & Obst. **111:** 103 (Aug.), 1960.

Thirteen technics for measuring various blood flows were discussed, and most were depicted. Included were the Fick principal and indicator dilution curves for cardiac output, the para-aminohippurate clearance for renal plasma flow, the bromsulfonephthalein clearance for hepatic blood flow, and occlusion plethysmography for extremity blood flow. Methods for estimating flow in an individual vessel, ordinarily in experimental circumstances, were simple cannulation with measurement of the outflow, the Stromuhr of Ludwig, the bubble flowmeter, the orifice flowmeter, the turbine flowmeter, and the rotameter. Noncannulating methods were the thermostromuhr of Rein, the electromagnetic flowmeter, and the ultrasonic flowmeter. The shortcomings of existing technics, especially those for clinical use, were described, and a prediction of forthcoming improvements was made.

ROGERS

Seki, I.: Clinical Pathophysiological Studies on the Relationship between Myocardial Oxygen Demand-and-Supply and Electrocardiographic Changes in Induced Anoxaemia. Japanese Circulation J. **24:** 695 (July), 1960.

The anoxemia test of Patterson and Levy was employed by the author to study possible correlations between electrocardiographic changes and other parameters, such as the intensity of the induced hypoxemia, general circulatory responses, cardiac strain, and, further, myocardial oxygen demand and supply. This study was made through the use of catheterization of the coronary sinus and of the right side of the heart. The height of T_{11}, T_{V4}, QRS-T angle, mean vectors, ventricular gradient, QT_C interval, and anoxemia index were analyzed. These studies were made in healthly control subjects, patients with pulmonary disease, acute and chronic hepatic disease, cardiac disease, and in patients with sclerotic vascular disease. T-wave inversions and S-T depressions have been the approved index of coronary insufficiency in this test. It has been accepted that these changes have resulted from a disparity between supply and demand of the coronary flow. The changes of coronary insufficiency in the anoxemia test appeared to be due to a reduced myocardial oxygen consumption and not necessarily related to diminution in coronary flow. In normal subjects or those with pulmonary disease arterial oxygen saturation was highly correlated with significant electrocardiographic changes. In patients with coronary disease this correlation did not hold, probably because of the difference in coronary flow in the latter. Electrocardiographic changes were found to be influenced by the strain a heart must undergo in its circulatory adjustment associated with the induced anoxemia. Positive tests in noncoronary patients may be due to anemia, emphysema, or certain cardiac anomalies. Patients with hypertension may also show a positive anoxemia test due to the disproportion between the cross section of the coronary blood vessels per unit cross section of cardiac muscle. In patients with liver disease a positive test is held to be due to the impaired oxidative system of the heart muscle due to abnormal protein metabolism. A negative anoxemia test in the

face of coronary disease is explained on the basis that this group exhibited lesser degrees of myocardial tension in their circulatory adjustment to the anoxemia. Therefore, close attention must be paid to the cardiovascular response in interpretation of the anoxemia test. When possible, arterial oxygen saturation and the magnitude of anoxemia stress must be measured and the electrocardiogram interpreted in the light of these factors. There was a high correlation between heart rate and electrocardiographic changes in the anoxemia test. Tachycardia shortened diastole and elevated the myocardial tension uneconomically. In cardiovascular diseases this unfavorable influence was not sufficiently compensated by an increase in coronary flow or myocardial metabolism due to coronary sclerosis or myocardial involvement.

LEVINSON

Sharp, J. T., Bunnell, I. L., Holland, J. F., Griffith, G. T., and Greene, D. G.: Hemodynamics during Induced Cardiac Tamponade in Man. Am. J. Med. 29: 640 (Oct.), 1960.

Hemodynamics were studied in a patient with bronchogenic carcinoma with pericardial invasion and rapid accumulation of pericardial fluid. Cardiac catheterization was performed with a double-lumen Cournand catheter placed in the right atrium and right ventricle. Variable amounts of saline solution were introduced into the pericardial sac with measurements made before, during, and after the procedure. There was a marked discrepancy between respiratory fluctuations in the pulmonary wedge pressure on the one hand and the pericardial sac on the other hand. Increasing pericardial pressure caused a further decrease in inspiratory filling gradient and a decreased stroke volume. Similar fluctuations on the pulmonary side were thought to represent direct transmission of intrathoracic pressure to the vasculature of the lungs because of greater pleural pressure swings.

KALMANSOHN

Stern, W. E., and Good, R. G.: Studies of the Effects of Hypothermia upon Cerebrospinal Fluid Oxygen Tension and Carotid Blood Flow Surgery 48: 13 (July), 1960.

The effects of total body cooling in cats and monkeys were studied using the polarographic technic of determining cisternal cerebrospinal fluid oxygen availability and the electromagnetic blood flow principle to determine carotid blood flow. Carotid blood flow fell disproportionately more than did systemic arterial blood pressure as the body temperature fell. Cisternal oxygen availability, assumed to reflect oxygen diffusing from the arterial system into the fluid environment of the cerebral tissue, fell as the animal was cooled; but the percentage of fall was less than the fall in carotid arterial flow below 31 C. (brain temperature) in monkeys and 29 C. in cats. It was suggested that this decreased untilization of oxygen by the tissues protected the brain against other circumstances which might produce anoxia. In addition, the normothermic responses of blood pressure and cisternal oxygen tension to ischemic and anoxic anoxia were sharply reduced at hypothermic levels, suggesting decreased sensitivity to and probably increased tolerance to anoxia. The authors considered that the brain is maximally protected against anoxia at body temperatures below 31 C.

SHEPS

Waldhausen, J. A., Braunwald, N. S., Bloodwell, R. D., Cornell, W. P., and Morrow, A. G.: Left Ventricular Function following Elective Cardiac Arrest. J. Thoracic Surg. 39: 799 (June), 1960.

The effects of cardiac arrest on left ventricular function were studied in 44 dogs. Left ventricular function was determined by relating left ventricular stroke work to mean left atrial pressure. The effect of the arresting agent was determined by a comparison of the control and post-arrest curves in each experiment. These could not be related to any simple mathematical index and it was apparent that the results of the experiments described did not lend themselves to quantitative analysis. There was abundant evidence, from the marked qualitative differences in the curves, that cardiac arrest induced for more than 10 minutes with either potassium citrate or acetycholine was almost uniformly associated with subsequent severe depression of myocardial function. Continuous aortic occlusion for 10 to 20 minutes was responsible for only moderate impairment of function, and intermittent aortic occlusion caused no significant depression when continued for 30 minutes. It would appear then that the latter technic, without the perfusion of cardioplegic agents, is the technic of choice for open cardiac operations not necessitating prolonged aortotomy. In those requiring prolonged aortotomy for extended periods, direct selective coronary perfusion has been found the technic of choice.

LEVINSON

Wang, Y., Marshall, R. J., and Shepherd, J. T.: The Effect of Changes in Posture and of Graded Exercise on Stroke Volume in Man. J. Clin. Invest. 39: 1051 (July), 1960.

Cardiac output, heart rate, and stroke volume were increased in four untrained male subjects at rest in the supine position, at rest standing, and during exercise in the upright position. When the patient stood there was a fall in cardiac output and stroke index and an increase in the heart rate. Mild or moderate exercise in the upright position increased the stroke index almost to the level obtained when the subject was at rest in the supine position and with heavy exercise it increased above the resting level. The authors conclude that the stroke volume increases only slightly once exercise has begun regardless of whether the subject is supine or upright, whereas this value varies considerably with body position when the subject is at rest.

KARPMAN

Warner, H. R., and Toronto, A. F.: Regulation of Cardiac Output Through Stroke Volume. Circulation Research **8**: 549 (May), 1960.

Atrial-ventricular conduction was interrupted surgically in seven untrained mongrel dogs. Heart rate was controlled thereafter by direct stimulation of the right ventriele. Cardiac output was measured by the indicator-dilution technic at various heart rates, while the animal was at rest *and while walking on a treadmill. In the unanes*thetized dog, cardiac output was independent of heart rate in the range of 90 to 240 beats per *minute studied. This was true also in the dog* performing mild exercise. Cardiac output, however, decreased significantly at both extremes of heart rate. It was concluded that cardiac output could be regulated to provide required flow through changes in stroke volume alone, even though adjustment of heart rate was the usual means for obtaining this end.

SCHIRGER

PULMONARY DISEASE

Endrys, J., Lukl, P., Ressl, J., Weinberg, J. and Zmeskal, A.: Peripheral Stenosis of the Pulmonary Artery with Pulmonary Hypertension. Cor et Vasa **1**: 47, 1959.

The patient described in this paper is the oldest person (38 years old) with peripheral pulmonary stenosis reported until now, and the first with a probably acquired origin. In this patient the stenosis could be demonstrated by means of angiocardiography; when the cardiac catheter was moved back and forth in the right pulmonary artery branch, the systolic pressure changed abruptly from 132 to 38 mm. Hg. The pulmonary hypertension could not be influenced by intravascular acetyl choline injection. The possibility of a shunt was excluded by indicator-dilution curves and by the results of oxygen saturation studies in the right heart. As the pulmonary arteries leading to the left lower lobe did not fill during angiocardiography, a pulmonary embolism which probably appeared under the clinical picture of pneumonia at the age of 23 would have accounted best for the peripheral pulmonary stenosis. Diagnostically important findings were a systolic murmur heard only over the right lung and wide splitting of the second sound; both were accentuated considerably during inspiration. These findings would have allowed the diagnosis even without cardiac catheterization and angiocardiography. The electrocardiogram showed marked right ventricular hypertrophy.

LEPESCHKIN

Gurtner, H. P., Briscoe, W. A., and Cournand, A.: Studies of the Ventilation-Perfusion Relationships in the Lungs of Subjects with Chronic Pulmonary Emphysema, following a Single Intravenous Injection of Radioactive Krypton (Kr 85). I. Presentation and Validation of a Theoretical Model. J. Clin. Invest. **39**: 1080 (July), 1960.

Radioactive krypton was rapidly injected intravenously in emphysematous patients and its behavior was studied in order to determine the distribution of perfusion in the lung. The authors present (1) a theoretical model of the lungs and tissues of the emphysematous patient, (2) a mathematical solution of the equations of the three-compartment (well ventilated alveoli, poorly ventilated alveoli, tissues) analog thus depicted, (3) a comparison of the predicted theoretical curves with the experimental curves which are actually obtained, and (4) three methods for interpreting experimental data in terms of dimensions, ventilation, and blood perfusion of several lung compartments. The behavior of the radioactive krypton in the various gases and blood streams of the emphysematous patient was predicted when the effective tissue volume was either 10 or 60 liters in the theoretical model and the behavior of the emphysematous patient resembled that predicted for the model. The authors also present a method for assessing the distribution of perfusion to the lung by the simultaneous measurement of expired, arterial, and mixed venous concentration curves; two other similar but less accurate methods for measuring these values are also presented and evaluated.

KARPMAN

NEWS FROM THE AMERICAN HEART ASSOCIATION

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Heart Association's Awards Presented at Annual Meeting

Among the honors conferred by the American Heart Association at its Annual Meeting and Scientific Sessions in Bal Harbour, Florida, were the following:

Gold Heart Awards

Gold Heart Awards, highest honor of the American Heart Association, were presented at the Association's Annual Dinner to Tinsley R. Harrison, M.D., Professor of Medicine, Medical College of Alabama, Birmingham, who was President of the American Heart Association from 1948-49; to Mr. Frank L. Mechem of Seattle, prominent attorney who served on the Association's Board of Directors for nearly a decade and as a Vice President from 1957-60; and to Louis N. Katz, M.D., of Chicago, Director, Department of Cardiovascular Research, Michael Reese Hospital, a past President of the Association (1951-52). They were cited for outstanding contributions in advancing the objectives of the American Heart Association.

Research Achievement Award

The Association's new Research Achievement Award for outstanding contributions to cardiovascular research was conferred on Charles H. Rammelkamp, Jr., M.D., Professor of Medicine, Western Reserve University School of Medicine, Cleveland. Dr. Rammelkamp, a Vice President of the American Heart Association, was cited for his many achievements in the field of streptococcal infections and their complications, including rheumatic fever and rheumatic heart disease.

Dr. Rammelkamp's studies in the group A streptococcus began in the 1940's shortly after the introduction of penicillin. In 1949, he organized and directed the Streptococcal Disease Laboratory in Cheyenne, Wyoming, focusing his efforts primarily on the streptococcus in its relationship to acute rheumatic fever and rheumatic heart disease. Under his leadership, the laboratory produced reports elucidating the epidemiology of streptococcal infections, the role of specific factors in the pathogenesis of acute rheumatic fever, and effective approaches to the control of rheumatic heart disease. In addition to his own research achievements, Dr. Rammelkamp's guidance, as Chairman of the AHA Research Committee and in other positions, has influenced the direction and greatly accelerated the pace of research throughout the cardiovascular field.

The AHA Research Achievement Award included an honorarium of $1,000 and an illuminated scroll.

Affiliates Donate Record $125,125 to National Research Program

Affiliates and chapters of the American Heart Association have contributed a record $125,125 to supplement the Association's national research program. These donations have made possible the support of studies approved by the AHA Research Committee for fiscal 1961-62 which could not otherwise be financed by the national research budget.

In addition to those previously reported, contributions in excess of amounts regularly assigned for research have been received from the following Heart Associations:

Norwalk (Conn.) Heart Association, $8,000 in partial support of grants to Drs. J. Francis Dammann, Jr., University of Virginia Charlottesville, and Michael Hume, Yale University School of Medicine.

Stamford-Darien-New Canaan (Conn.) Heart Chapter, $4,000 in partial support of grants to Drs. M. Jay Goodkind and Levin L. Waters, Yale University School of Medicine.

Idaho Heart Association, $3,840, for the continuing and partial support of grants to Drs. John J. Osborn, Institute of Medical Sciences, San Francisco, Robert F. Rushmer, University of Washington, Seattle, and Arthur J. Seaman, University of Oregon, Portland.

Illinois Heart Association, $21,900, in full support of Established Investigatorships to Drs. Ruth Pick, Michael Reese Hospital and Medical Research Institute, Chicago, and Victor Pollak, University of Illinois College of Medicine, Chicago.

Dental-Medical Education Committee Is Formed by Heart Association

A Committee on Dental-Medical Education, which will concern itself with mutual problems relating to cardiovascular patients, has been established by the American Heart Association.

Chairman of the new group, a subcommittee of the Association's Committee on Professional Education, is Lester W. Burket, D.D.S., Dean of the University of Pennsylvania Dental School, Philadelphia.

Serving with him are Thomas L. Louden, D.D.S., Washington, D. C., who is also liaison representative for the Heart Disease Control Program, U. S. Public Health Service; Henry D. McIntosh, M.D., Associate Professor of Medicine, Duke University School of Medicine, Durham, North Carolina, also serving as liaison for the American Dental Association; J. Roy Doty, Ph.D., of Chicago, Secretary of the American Dental Association's Council on Dental Therapeutics; and J. Paul Guidry, D.D.S., of Kirkwood, Missouri.

AHA Scientific Sessions Abstracts Are Obtainable in Volume Form

Abstracts of investigative work presented at the Scientific Sessions of the American Heart Association from 1955 through 1960 are available in volume form from local Heart Associations or the American Heart Association.

The volumes covering the 1955-57 period are $1.00 each. Those for the years from 1958-60 are $2.00 each. Abstracts presented at the 1954 AHA Scientific Sessions are included in a volume which also contains papers presented at the Second World Congress of Cardiology. These are obtainable at $1.50.

Also of interest to cardiologists, internists, medical scientists and medical libraries are transactions of the 1954 and 1957 Conferences on Cerebral Vascular Diseases held under AHA auspices. Edited by Irving S. Wright, M.D., E. Hugh Luckey, M.D., and Clark H. Millikan, M.D., these may be ordered from the publishers, Grune and Stratton, 381 Park Avenue South, New York 17, New York.

World Cardiology Congress Plan Outlined, Registration Dates Set

Plans are well under way for the Fourth World Congress of Cardiology, to be held from October 7-13, 1962 in Mexico City.

Dr. I. Chavez, President of the Organizing Committee and of the International Society of Cardiology which is sponsoring the Congress, in an announcement inviting cardiologists throughout the world to participate stated:

"We want to avoid too many papers being presented; we prefer a smaller number of them, subject to a very strict selection. We shall try not to let the Congress become broken up by a divergence of numerous and simultaneous sessions; on the contrary, we wish to have a maximum concentration and for that purpose there will be no more than four simultaneous sessions.

"We are also planning to have a greater number of symposia, panel discussions, etc., which will be entrusted to the best representa-

tives of our specialty, and enlightened by extensive discussions. Special opportunity will be granted to young investigators who can provide original contributions, but at the same time, good care will be taken neither to let cardiology become fragmented and lose its unity, nor to allow it to be disconnected from the general panorama of medicine."

Thus, those presenting papers are asked to bear in mind the Congress' purpose of integrating cardiology as far as is compatible with technical progress in individual fields.

Registration Dates Set

The Organizing Committee would like to know, as soon as possible, the number of persons who plan to attend the Congress and the type and amount of scientific contributions they wish to make. Therefore, two registration periods have been set as follows:

1: *Through December 31, 1961.* Members registering during this first period will be given priority in hotel accommodations, at the official Congress banquet and at social events. They will be granted free transportation to and from the airport and their hotels on arrival and departure, and from their hotels and the Congress throughout the meetings.

2: *Beginning January 1, 1962.* Those registering after this date, although they are assured of the maximum comfort available at the time, must accept whatever remaining accommodations are obtainable by the Organizing Committee.

Active Members will have the right to present papers and participate in scientific discussions and in all other social or cultural activities to be detailed in the program. In addition, there will be a category of *Associate Members,* who will be the relatives of Congress members. Although they will not participate in scientific or other sessions, Associate Members will be granted all other privileges of active members in addition to cultural and social programs especially designed for them.

Registrations may be made through Dr. I. Costero, Secretary General, Instituto Nacional de Cardiologia, Ave. Cuauhtemoc, 300, Mexico 7, D.F.

Proceedings of Conference On Angiotensin Available

The proceedings of a conference on "Mechanisms of Experimental Renal Hypertension," held last April in Augusta, Michigan, are now available in reprint form.

The program, with Sibley W. Hoobler, M.D., as Chairman and A. C. Corcoran, M.D., as Vice Chairman, included reviews of the following topics:

"Physiologic Mechanisms" (Renin, Liver, Adrenal, Kidney); "Vessel Wall Changes" (Reactivity of Arterioles, Arteriolar Rigidity, Effect of Hypertension on Vessel Walls); "Humoral Substances" (Antihypertensive Substance from Kidney, Anephrotensin, Angiotensin, Renin).

Copies are obtainable without charge from Walter Freyburger, M.D., the Upjohn Company, Kalamazoo, Michigan.

Meetings Calendar

November 13-18: Canadian Heart Association and National Heart Foundation of Canada, Annual Meeting and Scientific Sessions, Vancouver. J. B. Armstrong, National Heart Foundation of Canada, 501 Yonge St., Toronto 5, Canada.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

November 25-27: American College of Chest Physicians, Interim Session, Denver. Murray Kornfeld, 112 E. Chestnut, Chicago 11, Illinois.

November 27-29: American Society of Hematology, Los Angeles. John W. Rebuck, Henry Ford Hospital, Detroit 2, Michigan.

November 27-30: American Medical Association, Clinical Meeting, Denver. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

December 1-2: Symposium on Cinefluorography (3rd), Rochester, New York. Stanley M. Rogoff, University of Rochester Medical Center, Rochester 20, New York.

December 8-9: New York Heart Association, Symposium on the Plasma Membrane, New York. Alfred P. Fishman, 10 Columbus Circle, New York 19, New York.

1962

January 29-February 1: American College of Surgeons, Sectional Meeting, Los Angeles. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

February 3-6: Congress on Medical Education and Licensure, Chicago. W. S. Wiggins, 535 N. Dearborn, Chicago 10, Illinois.

February 7-10: American College of Radiology, New York. W. C. Stronach, 20 N. Wacker Dr., Chicago 6, Illinois.

February 8-10: Society of University Surgeons, Cleveland. C. F. Kittle, University of Kansas Medical Center, Kansas City 12, Kansas.

March 5-7: American College of Surgeons, Sectional Meeting, Detroit. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

March 26-28: American College of Surgeons, Sectional Meeting, Memphis. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

March 30-April 1: American Psychosomatic Society, Annual Meeting, Rochester, New York. Stewart Wolf, 265 Nassau Rd., Roosevelt, New York.

April 6-8: American Society of Internal Medicine, Philadelphia. G. T. Bates, 350 Post St., San Francisco 8, California.

April 6-13: American Academy of General Practice, Las Vegas, Nevada. Mac F. Cahal, Volker at Brookside, Kansas City 12, Missouri.

April 9-13: American College of Physicians, Philadelphia. E. C. Rosenow, Jr., 4200 Pine St., Philadelphia 4, Pennsylvania.

April 16-18: American College of Surgeons, Sectional Meeting, Washington, D. C. W. E. Adams, 40 E. Erie, Chicago 11, Illinois.

April 29: American Federation for Clinical Research, Atlantic City. J. E. Bryan, 250 W. 57th St., New York 19, New York.

May 1-2: Association of American Physicians (members only), Atlantic City. Eugene A. Stead, Jr., Duke Hospital, Durham, North Carolina.

May 29-June 2: American College of Cardiology, Denver. Philip Reichert, Empire State Bldg., New York 1, New York.

June 23: International Cardiovascular Society, North American Chapter, Chicago. R. A. Deterling, Jr., 171 Harrison Ave., Boston 11, Massachusetts.

June 25-29: American Medical Association, Annual Meeting, Chicago. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

1962 **Abroad**

September 5-8: International Congress of Internal Medicine, Munich. Prof. E. Wolheim, Luitpoldkrankenhaus, Wurzburg, Germany.

October 7-13: Fourth World Congress of Cardiology, Mexico City. I. Costero, Secretary General, Ave. Cuauhtemoc 300, Mexico 7, D.F.

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